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(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

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Medical
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THYROID HEART, A TRANSITORY CONDITION[1]

HENRY M. THOMAS, JR.

From the Thyroid Clinic, Johns Hopkins Hospital

Patients suffering from cases of hyperthyroidism occasionally die from heart failure. Severe myocardial decompensation is a frequent accompaniment of this disease but the exact cause of the heart failure and the method of pathological injury to the heart are unknown. The two cases here reported illustrate two outcomes (if not the only ones) of thyroid heart disease: (1) A patient who died of heart failure without adequate pathological explanation, and (2) A patient who presented evidence of extreme heart failure but whose heart's action returned to normal after the hyperthyroidism had been corrected by a subtotal thyroidectomy.

Case I. Mr. B., aged 49. From October 25 to November 1, 1927, he was in the Church Home and Infirmary (No. 44548), and was transferred to the Johns Hopkins Hospital November 1, 1927.

Present Illness. From the past history it is evident that the patient felt perfectly well until fifteen months ago. At that time the first thing he noticed was a feeling of fatigue, regardless of the fact that he was getting a normal amount of rest. About this time he also began to lose strength. In January he noticed a swelling of his neck and his wife called his attention to the prominence of his eyes. At this time he also noticed that he was short of breath on the slightest exertion. About nine months ago he began to feel extremely nervous at all times and was losing weight, despite the fact that his food consumption was normal. He consulted a physician who gave him Lugol's solution but with very little relief. Although he stopped active work in January, 1927, he has never gone to bed to stay for treatment until coming to Baltimore a little over a week ago. About three weeks ago the patient began to regain quickly his 35 pounds of lost weight but it was quite evident that the increased weight was due to an accumulation of fluid in his legs and feet. Two months ago he noticed that his abdomen was enlarging and, one week ago, that it was markedly distended with fluid. Three weeks ago he noticed that his heart was beating very irregularly and he had a sensation of something stretching inside his chest with each heart beat. About this time he became very

[1] Received for publication, December 20, 1929.

short of breath and was unable to sleep or rest at night. He states that he had not rested for two weeks previous to entering the hospital.

Physical examinations. The patient is a rather poorly nourished male, age 49, lying in bed in apparent discomfort. He is dyspnoeic and quite apprehensive; has a tendency to cry from worry and depression. Skin slightly pale, warm and moist. Hair prematurely white. Eyes: Well marked exophthalmos; Stellwag's and von Graefe's signs positive. There is a deposit of fat around the outer edges of the sclerae which have a subicteric tint. Pupils slightly dilated but react promptly to light and accommodation. Neck: Marked struma and increased vascularity. The whole mass pulsates. Well marked bruit. The thyroid is uniformly enlarged. Chest: Respiratory excursion equal on the two sides. Shallow and rapid rate of breathing. Percussion note resonant over lung fields. Moist râles are heard in both lower lobes. No bronchial breathing. Heart: Markedly enlarged. P.M.I. in 6th interspace. Sounds harsh. A moderate systolic murmur is heard at the apex. Rhythm absolutely irregular—auricular fibrillation with a pulse deficit of 12 to the minute. Aortic and pulmonic second sounds accentuated. Radial pulses equal on the two sides, quite irregular in force and rhythm. Blood pressure 136–124 over 86–72. Vessel wall normal and elastic. Abdomen: No particular tenderness on palpation. Liver edge extends about 6 cm. below costal margin. No oedema of abdominal wall. Spleen and kidneys not palpable. No masses nor rigidity. Evident free fluid in the abdomen with shifting dullness. Extremities show slight oedema.

October 29th, basal metabolic rate 44 per cent above the average normal for his age and sex (Weight 177 pounds). Urine: Sp. gr. 1015, Alb. +, Sug. O. Rare hyalin cast. R.B.C. 4,000,000. Hb. 70 per cent.

Course in Hospital. Digitalis therapy was instituted and Lugol's solution (M.X, t.i.d.) was given. Extreme diuresis occurred and in 15 days the patient lost 50 pounds. The basal metabolic rate fell only 9 points but correcting for the loss of weight of inert excess fluid, this drop would amount to nearly 30 points. During the next nine days, however, the basal metabolic rate went up 16 points and the patient's weight increased slightly.

X-ray showed a remarkably enlarged heart.

On November 22, 1927, a subtotal thyroidectomy was performed by Dr. W. F. Rienhoff, Jr. The post-operative course was usual until the morning of the third day. On November 25, the patient awakened from sleep, complained of precordial pain and breathlessness (pulse was 72 to the minute) and five minutes later he stopped breathing.

EXTRACT FROM AUTOPSY REPORT (NO. 10151)

Body: The body is that of a middle-aged white man. The general nutrition is fair. There is a moderate degree of rigor mortis. The conjunctivae and sclerae show no evidence of jaundice. The nose and mouth are normal. There is a heal-

ing wound of a thyroid operation. The chest is of normal contour. Abdomen not distended. External genitalia and extremities normal. There is no oedema.

Heart: The heart is distinctly enlarged; it weighs 460 grams. The epicardial surface is smooth. There are several small patchy thickenings of the epicardium. The coronary vessels show some patches of arteriosclerosis, but these are not very extensive. A medium-sized branch of the right coronary artery, as it enters the myocardium, is plugged by a fresh thrombus which completely fills the vessel; the heart muscle supplied by this vessel does not appear to be infarcted. The heart muscle is everywhere soft, flabby and not scarred. On section all the chambers of the heart are somewhat dilated as well as hypertrophied; the dilatation of the right auricle is especially marked. On section of the left ventricle the myocardium is more yellow than usual and on closer inspection some small indefinite flecks of grayish yellow are made out. No scars are seen. The valves are all soft and delicate. About the aortic valve there are some small sclerotic patches but the edges of the cusps are thin and delicate. The heart measurements are as follows:

Tricuspid valve	15 cm.
Pulmonary valve	9 cm.
Mitral valve	10 cm.
Aortic valve	7 cm.
Left ventricular wall	14 mm.
Right ventricular wall	4 mm.

The first part of the aorta is almost normal, showing only some fatty patches in the intima, but further down toward the bifurcation the degree of arteriosclerotic change becomes greater. Near the bifurcation there is considerable change in the intima with fibrous plaques and an occasional small area of calcification.

There is a distinct nodular cirrhosis of the liver.

The spleen is considerably enlarged and firm in consistence.

The left kidney shows several small infarcted areas in the cortex.

The other organs show no noteworthy alterations in the gross.

MICROSCOPIC NOTES

Heart: The heart shows little to account for the mottling seen in the gross. A frozen section shows no fat. There is only a very slight increase in connective tissue about a few vessels. A slight infiltration of polymorphonuclear leucocyctes and mononuclear cells between strands of fibers is seen in one area. There is a small fresh thrombus in the vessel described in the gross examination.

Liver: The liver shows a definite cirrhosis. The scars are moderate in extent and the blood vessels are fairly well filled with blood.

Adrenal normal.

Hypophysis: Poorly fixed. A little stratified epithelium is seen along the side of the stalk.

Thymus: There is very well preserved thymus tissue containing many lymphocytes and, although not increased in bulk, it seems to be rather definitely hypertrophic.

Kidney: One kidney shows a fresh infarct which seems to have occurred in segments with a narrow zone of hemorrhage and polymorphonuclear leucocytes between these. Another section shows an almost normal kidney.

Thyroid: The thyroid, in the portion removed at operation, shows rather characteristically the appearance typical of exophthalmic goiter with large alveoli accompanied by smaller ones, irregular in outline with rather high, but not very high epithelium. There is a good deal of colloid in these alveoli. There are no nodules scattered through the thyroid.

From this report one may surmise that the immediate cause of death was the occlusion of a very small coronary artery, so small in fact that it could hardly have produced death in any case except one in which the heart was already in an extremely precarious condition. It seems probable that the fresh thrombus in the coronary artery, as well as the thrombi responsible for the fresh renal infarcts, were emboli from the dilated heart although no mural thrombi were noted at autopsy. The microscopic examination of the heart revealed only very minor abnormalities and the main changes seem to have been marked cardiac dilatation and slight hypertrophy.

Case II. Mr. G., aged 44 years. Occupation: Railway track laborer. Admitted to the Church Home and Infirmary December 30, 1926.

Nervousness and prominence of the eyes had been first noticed about 14 months before admission. Five months previous to admission (March, 1926) a local physician had diagnosed his case as exophthalmic goiter, but he was given no treatment. In April he suddenly lost his voice and this condition lasted three months after which it gradually disappeared. During the summer months the nervousness increased and he had several attacks of diarrhoea. His wife noticed that his appetite was abnormally good but that he was becoming tremulous. About 7 weeks before admission dyspnoea, orthopnoea and palpitation became very marked and there was some cough and slight swelling of the ankles. There was no past history of tonsillitis, chorea, rheumatism or symptoms suggesting syphilis, the only previous illness being typhoid fever in 1916.

Physical examinations. A well developed man of 44 years, weighing 160 pounds. He was very restless although not apprehensive. His skin was flushed and moist. There was an extreme degree of exophthalmos of both eyes which had resulted in an inflammatory condition of the conjunctivae. The thyroid was diffusely enlarged, rather soft in consistence with no thrills or bruits. Cardiac dullness measured 5 cm. to the right of the midline and about 9 cm. to the left. The sounds at the apex were quite irregular (108 to the minute) and a systolic murmur was heard. The sounds at the base were irregular; no murmurs. There was a pulse deficit of 17 beats to the minute. Blood pressure 150/70. Lungs clear, no râles at

the bases. Liver not felt. Marked tremor of the extended fingers. Slight oedema of the ankles.

Basal metabolic rate 95 per cent above the average normal for his size, age and sex (December 31, 1926). Urine: Acid, 1020, Alb. +, Sug. 0, Micro: Normal. Haemoglobin 95 per cent.

Course in the Hospital. Digitalis therapy was instituted and Lugol's Solution (m.X, t.i.d.) was given. Marked symptomatic improvement took place with a corresponding fall in the basal metabolic rate to +32 on January 6th (weight 154 pounds) and to +14 on January 11th (weight 158 pounds). On January 14th a subtotal thyroidectomy was performed by Dr. W. F. Rienhoff, Jr., without altering the patient's condition to any extent. The Lugol's solution was discontinued (as is our usual procedure) and eleven days after the operation the B.M.R. was +35 per cent. Auricular fibrillation persisted but the patient was forced to return to his home in West Virginia on January 26th. From the history of his symptoms during the next twelve and a half months it seems evident that auricular fibrillation persisted uninterruptedly. He took tincture of digitalis under the direction of his local physician. In May he resumed his work, but he could not do more than pump the hand-car out to work and he often became short of breath. He was somewhat better during July but in August he began to get nervous and run-down and could not walk 300 yards without breathlessness. He rested during September and improved slightly, but could only perform an occasional day's work during October, November and December. Some time about the middle of December his condition began to go down-hill and in February he noticed a good deal of swelling of the legs. On his return to the hospital, *February 15, 1928*, he presented the picture of severe cardiac decompensation with auricular fibrillation, anasarca, (weight 195 pounds), liver palpable 6 cm. below the costal margin and cardiac dullness 4 cm. to the right and 15 cm. to the left in the sixth inter-costal space. Blood pressure 112/85. As the time the patient could stay in the hospital was extremely limited, digitalis and quinidin therapy were started simultaneously and 8 days later, during which time he had lost 33 pounds, the liver had become normal in size, and the pulse regular in force and rhythm. During the following week he continued to excrete the oedematous fluid until at the end of fourteen days after admission he had lost 42 pounds. Auricular fibrillation reappeared when the dose of quinidin was reduced, but normal rhythm was permanently restored by adding a dose of quinidin at midnight. The patient was discharged on *March 24th, 1928*.

He returned to Baltimore on *June 7th, 1928*, for examination. He said that he had taken tincture of digitalis (m.X, t.i.d.) and quinidin sulphate (grains V, t.i.d. and at 11 p.m.) regularly and had had no return of the irregular pulse. His strength had gradually increased so that he felt he was ready to resume work. He looked quiet and strong. There was no oedema: liver not palpable: no râles at the lung bases. Heart dullness 2 cm. to the right and 11 cm. to the left with a short, soft systolic murmur heard at the apex. Sounds regular and of fair quality,

although the first sound was somewhat muffled at the apex. B.M.R., −1 per cent. Weight 157 pounds.

The following report was given by Dr. E. C. Andrus from the Medical Service at the Johns Hopkins Hospital:

Electrocardiograph: June 7, 1928. Rate 67, Rhythm sino-auricular, P-R interval 0.23 second.

Remarks: T I, II and III inverted.

Diagnosis: Normal sinus rhythm. First degree heart-block. Sinus arrhythmia.

The first degree heart block as well as inversion of T I and II and the sinus arrhythmia are almost certainly due to the amount of digitalis which he had taken.

The teleoroentgenogram report was as follows: MR 5, ML 9, T 30. Aorta slightly dilated. Clinically, I should call his heart at present normal. The effect of exercise does not pass off as rapidly as is usual, (he carried a pulse rate of 90 to 95 fifteen minutes after hopping 50 times), but at the same time I could make out no organic lesion.

The patient returned home, discontinued all medication and three weeks later began work in the garden. He gradually increased his daily work until on September 12th, 1928, he returned to his full work as a track man on the railroad. Since that time he has done full manual labor without the loss of a single day from sickness. He arises at 5 a.m., makes the fire, milks a cow; breakfasts at 6; walks a mile to work which begins at 7.30 and lasts until 5; has a half hour for lunch. During this time the work is fairly constant with a pick or shovel. He usually returns home in a machine and retires at 8 p.m. He has noticed no swelling of the feet, no shortness of breath or irregularity of heart action; his appetite has been very good but not excessive and his weight has remained constant.

At my request the patient returned for examination.

Physical examination. March 2, 1929. 5 feet 11 inches; 162 pounds. There is quite definite exophthalmos, not as marked as on the previous examination but still very evident. The sclera of the left eye is injected; conjunctivae not inflamed.

Thyroidectomy scar barely perceptible. No thyroid tissue felt.

Lungs clear to percussion and auscultation; no râles at the apices or bases.

Heart: The apex is not clearly seen or felt. Dullness extends 8 cm. to the left of the midsternal line, 2 cm. to the right. No increase in dullness at the base. At the apex the sounds are clear, of good quality; no murmurs. No murmurs at the base.

Pulses are equal, synchronous and regular in force and rhythm; 17 to the quarter. The vessel wall is not thickened; brachials not tortuous. Blood pressure 120/80.

Liver not felt nor enlarged to percussion. Spleen not felt.

Extremities: No oedema of the ankles; no fine tremor of the fingers.

B.M.R.,—7 per cent.

Urine: Negative.

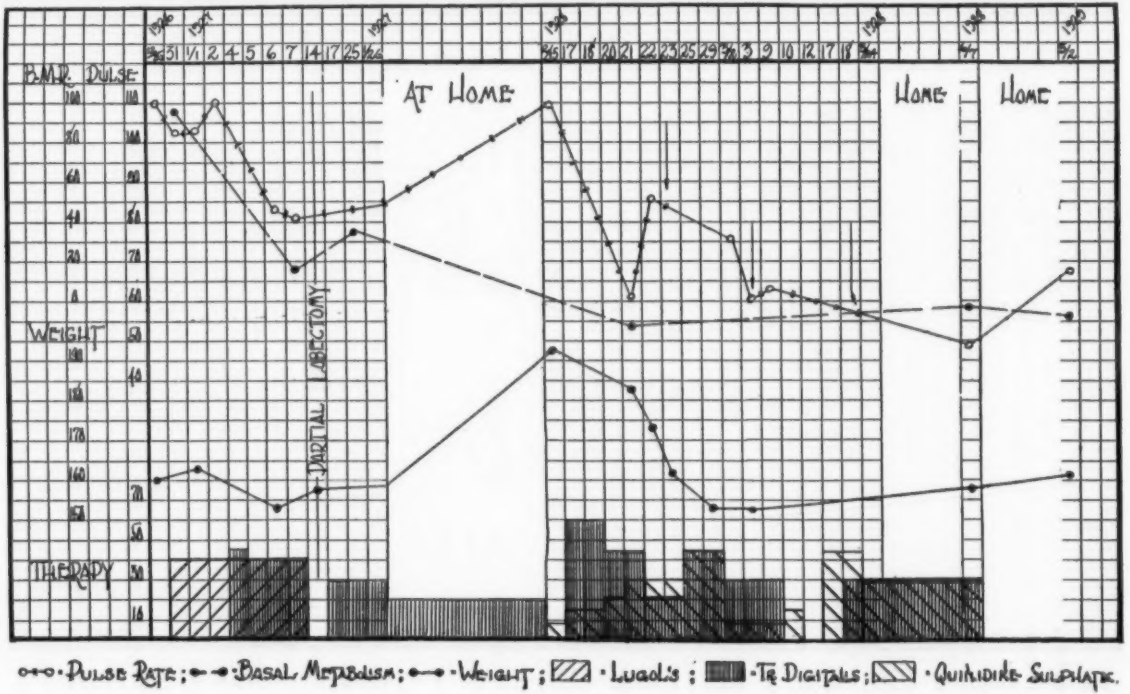

CHART I. CASE II

Following the partial lobectomy the patient insisted on returning home before the auricular fibrillation had been interrupted. During the 13 months at home on digitalis, under the direction of his local physician, he continued to fibrillate and gradually went down hill. During his second stay at the hospital on rest, digitalis and quinidin, he excreted 33 pounds of fluid in 8 days and reverted to normal rhythm on the 8th day. Since September 12, 1928, he has done full manual labor as a track man on the railroad without the loss of a single day from sickness and without taking either digitalis or quinidin. (This chart was drawn by Mr. Charles McCurdy Gray, a member of the graduating class of the Johns Hopkins Medical School.)

Electrocardiograph: March 2, 1929. Rate 76, Rhythm sino-auricular, P-R interval 0.30 second. Remarks: T waves all upright. P II diphasic. Diagnosis: Normal sinus rhythm.

DISCUSSION

Descriptions of the anatomical changes found in patients dying of thyroid heart disease are universally lacking in evidence of permanent heart damage. Changes that have been described (1) are (*a*) ***Marked cardiac dilatation***, usually most marked on the right side, (*b*) ***Slight cardiac hypertrophy***, (*c*) Variable, slight degrees of scattered perivascular ***round-cell infiltration*** (2). (*d*) ***Hyaline and fatty degeneration of the muscle fibers***. The first two of these changes may be the result of the long, constant over-work caused by hyperthyroidism (3). Perivascular round-cell infiltration, which has been found in some cases and not in others, is a matter of minor interest as it can hardly interfere with the action of the heart muscle nor can it, after healing, yield lesions which would alter the heart functionally. Actual changes in the muscle fibers themselves have been described by Wilson (1), Goodpasture (4), Goodall (5), Johnson (6), and others; but these and many other observers agree with the statements of Willius, Boothby and Wilson (7): "At necropsy insufficient evidence is disclosed to ascribe death to cardiac causes. Although in most cases degenerative changes were found, they could not be considered the dominant factor producing death. The finding of fatty degeneration of the heart, which in some cases is no more than that found in persons who die of old age, appears to be an expression of the effect of a long-continued or intense toxaemia, combined with increased activity."

Clinical observations (8) (9) on cases of thyroid heart disease have demonstrated (*a*) tachycardia, (*b*) enlarged heart, (*c*) congestive heart failure, (*d*) arrhythmia, usually auricular fibrillation, but occasionally flutter or heart-block (*e*) and variation in height and form of the T wave in electrocardiograms (10) (11). All of these signs may develop in an over-worked heart, but variations in tone of the regulatory cardiac nerves (vagus and sympathetic) may also account for some of them (11).

One wonders whether thyroxin, an excess of thyroxin, may cause various arrhythmias in some manner similar to the precocious systoles and attacks of paroxysmal tachycardia and paroxysmal auricular

fibrillation which some people experience following the use, or excessive use of tobacco and coffee. However that may be, it seems fairly clear that the effect of thyroxin on the heart is temporary and that no changes are produced which may not disappear when the hyperthyroidism subsides (12). We have seen no reason for believing in the theory of cardiac damage from the presence of a so-called adenoma of the thyroid or from long continued mild hyperthyroidism. This theory probably results from observations on middle-aged and elderly hyperthyroid patients (13), whose heart-changes were of some origin other than hyperthyroidism (14) but whose symptoms became more apparent in the presence of even mild hyperthyroidism.

SUMMARY

Two quite similar cases of exophthalmic goiter with severe myocardial insufficiency are reported. One patient died after operation on the thyroid gland while the other achieved complete clinical recovery. This second case then, an extreme form of myocardial insufficiency in thyroid heart disease with auricular fibrillation of more than a year's duration, which went on to subsequent complete recovery, demonstrates clearly the fact that even the most severe intoxication from hyperthyroidism need not produce permanent functional cardiac damage. In the first case, as in most others reported in the literature, although death resulted from heart failure, there was no evidence, pathologically, of significant myocardial damage. These cases, coupled with many others from this as well as from other clinics, place the burden of proof on those who claim that permanent myocardial damage results from hyperthyroidism.

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HISTOLOGICAL CHANGES IN NERVE CELLS FOLLOWING INJURY[1]

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INTRODUCTION

It is important to have certain definite criteria by which relative damage to nerve cells may be judged. Can cells having the potentialities of recovery be distinguished histologically from cells injured beyond repair in a subject dying immediately following a cerebral insult? This report is concerned with the analysis of nerve cell changes after one specific type of injury.

Material from the central nervous systems of 286 rats, subjected to contact with either alternating or continuous electric circuits at different potentials, has been studied to determine the amount of damage produced by electricity in the brain and cord (Langworthy and Kouwenhoven, 1930; Langworthy, 1930). Quite apart from this problem, such a quantity of well fixed and well stained sections makes it possible to discuss the possible pathological changes that can be demonstrated in nerve cells with the standard staining methods at present available. The abnormalities may occur in the nucleus or in the cytoplasm of the cell.

The cytoplasm of nerve cells normally contains numbers of bluish granules which are evident in fixed material stained with basic dyes. They constitute what is known as the Nissl substance. These granules are not demonstrable in live nerve cells (Bayliss, 1920); this statement may be verified by placing a bit of tissue from the ventral columns of the cord of a freshly killed animal upon a slide and staining with methylene blue. The cytoplasm of the nerve cell appears perfectly homogeneous. As the cell dies, the granules begin to appear in the cytoplasm. It is believed that the Nissl substance is produced after death by the precipitation of protein substances normally present in

[1] Received for publication February 26, 1930.

the cytoplasm (Marinesco, 1912; Mott, 1912). Recently, it has been shown that different fixatives alter, to a certain extent, the size and arrangement of the granules (Hopkins, 1924). The Nissl substance is normally utilized in cell metabolism. If an animal is killed after a long period of rest, the granules are abundant; when the animal is fatigued, the granules in the cytoplasm of the nerve cells are sparse.

As regards the normal nucleus of the nerve cell, it is large and clear, containing one or more nucleoli. The chromatin is small in quantity and arranged in fine interlacing strands.

The papers dealing with pathological changes in the nerve cell are legion; Barker (1909) gives a summary of the earlier work, while Buzzard and Greenfield (1925) bring the subject up to date in their recent textbook of neuropathology.

Perhaps, the best known change is that following avulsion of motor nerves. The abnormalities in the cells are most marked when young animals are used for the experiment. The changes are known as chromatolysis. At first, the Nissl granules swell and coalesce; later they are lost. The nucleus comes to occupy an eccentric position close to the edge of the cytoplasm. If the nerve fibres regenerate and regain functional connections with the muscles, restitution of the cell structure occurs; if they do not, total atrophy and disappearance of the cell may follow after a variable time.

Certain toxins and poisons such as arsenic, phosphorus and veratrin produce injury in the nerve cell, first demonstrable as a loss of Nissl substance. Sometimes, this change is more marked around the edges of the cytoplasm; at other times around the edge of the nucleus.

Anemia of the central nervous system likewise produces demonstrable changes in the nerve cells (Gomez and Pike, 1909). In the case of the medulla, according to these observers, anemia for twenty to thirty minutes produced anemia incompatible with complete recovery. After periods of severe anemia, the perivascular spaces were two or three times their normal size. The granules in the cytoplasm showed two types of lesions. In the large cells, there was often a clumping of the Nissl substance or a diffuse blue staining. Small cells seemed to lose their affinity for the stain. The granules were pale and diminished in number. Vacuolization of the cytoplasm occurred when the period of anemia was long and the animal had sur-

vived several hours. Sometimes the nucleus was slightly displaced. The nucleus often stained a diffuse blue and the outline was irregular and shrunken.

Mott and Uno (1922) studied the central nervous system of patients that died from surgical shock from 24 to 48 hours after the injury. The brains were fixed first in formalin and afterward the blocks were placed in alcohol. In the cerebellum very few Purkinje cells showed a normal staining reaction. The Nissl granules were broken up into fine dust, the cell was swollen, the nucleus indistinct and the whole cell only faintly stained. In the neighborhood, one could see cells presenting a more normal appearance. There was also a variable degree of chromatolysis, more marked in the autonomic nuclei of the medulla and less obvious in the somatic motor nuclei. The cells of the cerebral cortex were injured.

The possible types of changes that may be observed in the nerve cells after fixation and staining with the basic dyes do not present an infinite number of possibilities. As regards the cytoplasm, it often appears shrunken and surrounded by a large perivascular space. The Nissl granules may be swollen, clumped or lost; the loss may occur throughout the cytoplasm or be more marked around the edges of the cell or close to the nucleus. Often the cytoplasm stains a uniform blue color and no specific granules can be distinguished. Vacuolization of the cytoplasm has been described. Fracture of the cell membrane allows granules to escape and lie free in the perivascular space.

The nucleus is usually found in the center of the cytoplasm. Under abnormal conditions, it often shifts its position to one edge. The nucleus may become shrunken, leaving a clear surrounding area which indicates its normal size Frequently the nucleus stains a deep blue color so that the chromatin and nucleolus cannot be distinguished. The nucleolus is very resistant to injury, swelling, atrophy and fragmentation of the nucleolus have been described.

Hodge (1892) studied the changes produced in nerve cells by fatigue; he used most careful technique in the experiments. After seven hours' continuous stimulation of the nerve, the nuclei of the cells showed a decrease in size and a change from a smooth and rounded to a jagged, irregular outline. There was a loss of the reticulated appear-

ance of the nucleus with a deeper staining of the whole structure. The cytoplasm showed vacuolization, with shrinkage in size, and enlargement of the perivascular lymph spaces. After rest, the nucleus and cytoplasm gradually recovered their normal appearance. The protoplasm recovered rapidly so that within six and a half hours there was no vacuolization. Recovery of the nucleus was not complete for twenty-four hours. The shrinkage of the nucleus was directly proportional to the duration and intensity of stimulation.

Dolley (1911) likewise found that fatigue caused shrinking of the nucleus and cytoplasm of the nerve cell and that a rounding out of the cell and return of chromatin in the nucleus indicated recovery. He believed that, after severe stimulation, complete recovery of the nerve cells could not be expected for days.

The interpretation of pathological changes in nerve cells as seen in sections stained with a basic dye offers considerable difficulties. The types of abnormalities recorded by different observers have already been discussed. But before any observations may be considered valid, certain very definite postulates have to be fulfilled.

In the first place, in order that the finer structure of cells, and particularly of nerve cells, may be demonstrated, it is extremely important that the fixation of the tissue be carried out immediately after death. If the autopsy is delayed for only a few hours, the nerve cells tend to stain a uniform blue color with the basic dyes.

Moreover, the fixative is of importance. Hopkins (1924) found that the appearance of Nissl substance in fixed preparations of the ventral horn cells of the adult rat was largely dependent on the substances used for fixation. Zenker's fluid without acetic acid showed it as a diffuse granular substance in the cytoplasm. In some cells, after this fixation, slight concentration of the material was observable. The presence of acetic acid in the fixative caused the Nissl substance to appear as well defined bodies which increased in size with the amount of acetic acid used up to 10 per cent. He also studied other fixation methods.

In the present experiments 95-per-cent alcohol was used as a fixative; it insures a sharp, clear staining of the Nissl substance. Formalin, the standard fixative for nervous tissues, permits only a poor differentiation of the granules. However, the 95-per-cent alcohol does

not penetrate well, so that with fairly large brains an arterial injection is important. The central nervous system of the rat, on the other hand, is so small that in the present series the brain was not injected, but was cut instead in thin slices and immersed in the fixative.

It is often difficult to obtain a specimen of dye that will stain the granules well. A good thionin dye becomes slightly metachromatic and imparts to the granules a deep blue tint with a trace of lavender. The sections with this lavender hue do not fade easily and remain in good condition indefinitely. If the sections are overstained, the cytoplasm of the cells is of a uniform blue and the granules are not distinct; if the stain is light, the granules do not receive their full value.

After a sharp staining of the cells, of their nuclei and of the granules in the cytoplasm has been obtained, the interpretation still offers difficulties. Different groups of cells show great variation as to the size shape and the arrangement of the granules. Malone (1912, 1913 and 1929) has studied the characteristic pattern of the Nissl substance in certain groups of cells. Somatic motor cells have large granules packing the cytoplasm of the cell. Autonomic cells, on the other hand, have large granules around the edge of the cytoplasm and smaller granules in the remaining area. Sensory cells have fine, dust-like granules scattered uniformly. The possibilities of granule patterns in the higher centers of the brain are infinite. The present paper discusses only the somatic motor cells of the anterior horns of the spinal cord.

OBSERVATIONS

The present material is particularly valuable for study inasmuch as the central nervous system was placed in a suitable fixative immediately after the death of the rats. Moreover, good fixation is particularly easy to obtain in dealing with such a small brain. The staining of the sections was quite satisfactory. Finally, the large amount of histological material makes it possible to trace all stages in the injury, death or recovery of the cells.

Different harmful stimuli such as fatigue, anemia, metallic poisons and toxins acting on nerve cells cannot produce lesions that are absolutely unique for each type of injury, inasmuch as the criteria for discriminating the pathological lesions one from the other are so few.

For this reason, it is thought that the abnormalities following the electric injury are characteristic for injured nerve cells, no matter what the inciting cause.

The changes found in the cells are very similar to those seen by other workers and summarized in the introduction. However, a new question arises out of the problem of the electrical injuries. Is it possible, in the case of an animal which dies as an immediate result of an electrical shock, to distinguish the cells having in themselves the possibilities of recovery from those which have not? This is truly important in any attempt at a pathological study of the nervous system.

DESCRIPTION OF FIGURES

These somatic motor cells from the ventral horn of the spinal cord are stained with thionin, a basic dye.

FIG. 1. A normal ventral horn cell.

FIG. 2. Ventral horn cell with shrunken cytoplasm and a loss of granules, particularly on one side. The remaining Nissl substance is finely granular.

FIG. 3. The nucleus stains a uniform deep color and is greatly shrunken; it lies at one side of the cytoplasm and is surrounded by a clear area indicating its former size. The nucleolus cannot be distinguished. The Nissl substance has a coarsely granular, abnormal appearance.

FIG. 4. This cell is from a rat that survived the electric shock for six hours. The nucleolus is swollen and the cytoplasm stains a uniform deep color in which no granules can be made out.

FIG. 5. Hemorrhage compressed this anterior horn cell. The nucleus is displaced to one side. Granules are present at the edge of the cytoplasm but the center is quite free from them.

FIG. 6. This shows further recovery of the anterior horn cell. The nucleolus is swollen. One side of the cytoplasm is vacuolated and quite free from Nissl substance.

FIG. 7. The nucleolus is swollen and large vacuoles are present in the cytoplasm.

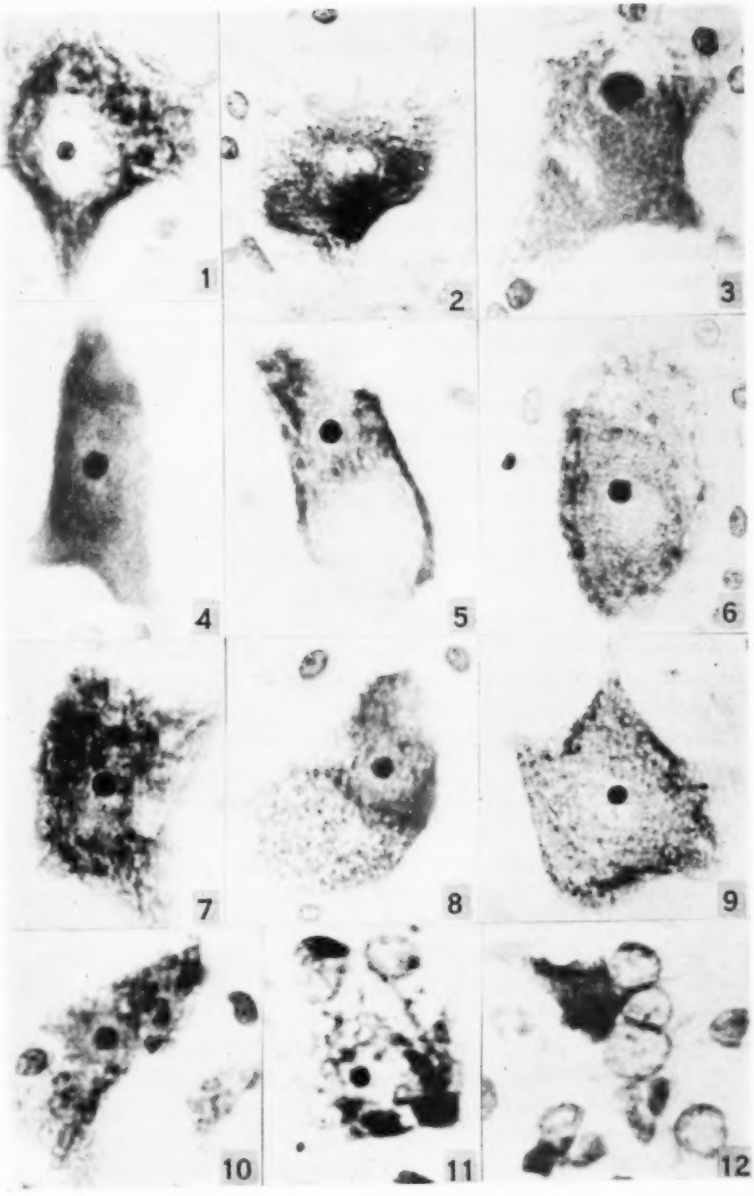
FIG. 8. Granules are abundant in the cytoplasm around the nucleus but the outer portions are quite free from them. This lightly staining area has a foamy, vacuolated appearance.

FIG. 9. In this cell granules are present around the edge of the cytoplasm, while the central area is quite free from them.

FIG. 10. The nucleolus is swollen. The cytoplasm stains deeply, but the granules are poorly defined. A phagocytic cell lies in the substance of the cytoplasm.

FIG. 11. The cell has a normal nucleus but the cytoplasm is vacuolated and contains few granules. Two phagocytic cells are attacking the nerve cell.

FIG. 12. The cell is greatly shrunken and stains a uniform deep color. It is surrounded by phagocytic cells.



FIGS. 1–12

As regards the actual experiments with electrical injuries very little need be said. Contact with continuous circuits produced greater injuries to nerve cells than did contacts with alternating circuits. Most of the pictures that illustrate the paper were taken from sections of the spinal cord of rats subjected to contact with a continuous circuit at 1000 volts potential for fractions of a second. No rats survived this current application for one second or longer.

Types of nerve cell injury are shown in the plate; the cells are all somatic motor cells from the ventral horns of the spinal cord. A normal anterior horn cell is shown in Figure 1. The nucleus which lies in the center of the cell is large and regular in outline. A nucleolus stains deeply in the nucleus and threads of chromatin may be seen. The cytoplasm of the cell is packed with large granules which stain clearly with the basic dye. These granules extend out into the dendrites.

The cell in Figure 2 is from a rat which died as an immediate result of an electrical injury. The nucleus is smaller than that of the normal cell and the outlines are irregular. The nucleolus is small; strands of chromatin may be seen in the nucleus. The nucleus occupies its normal central position. The cytoplasm is shrunken and the perivascular space enlarged. On one side, the granules are fairly numerous, while on the other side of the nucleus very few granules are seen. The cytoplasm in the latter position has a foamy appearance. The granules that remain, do not appear normal; they are smaller and dust-like.

The next cell (Fig. 3) from the cord of another rat which died immediately following the shock is obviously more severely injured. The nucleus does not lie in the center of the cytoplasm, but at one edge. Moreover, it is greatly shrunken, irregular in outline, and stains a uniform dark color. No nucleolus or chromatin strands can be distinguished. The nucleus is surrounded by an unstained halo which probably indicates its normal size. The cytoplasm is shrunken and the perivascular space enlarged. At the upper edge of the photograph, it almost looks as if the edge of the cytoplasm had burst into the perivascular space. A considerable amount of Nissl substance is present in the cytoplasm, but its appearance is different from that of the normal cell (Fig. 1) in that it is more homogenous and less light

and flaky. During the study of this material it was concluded that this type of cell with dark pyknotic nucleus no longer had the potentialities of recovery and even if the animal survived the shock this cell would die.

An anterior horn cell from a rat which survived the electrical injury, and was killed at the end of six hours, is shown in Figure 4. The cell is shrunken and has assumed a fusiform shape. The nucleolus is greatly swollen. The remainder of the nucleus is small and irregular, but of a normal pale color. The entire cytoplasm stains a deep blue with the basic dye, but no well-defined granules are present. After such a severe injury, the granules do not become normal in less than 48 hours. The first step in recovery is this uniform staining of the cytoplasm. Further steps in restitution of the cells will be described.

After many of the electrical injuries, large hemorrhages in the spinal cord appeared as direct sequelae. The hemorrhage introduced a new factor of injury, direct pressure upon the anterior horn cell. The cell in figure 5 was subjected to this pressure; the rat survived the electric shock for 3 days. The nucleus lies at one edge of the cytoplasm and is slightly swollen. Moreover, the edges of the nucleus cannot be clearly defined. Around the outer edge of the cell rather normal Nissl substance is present, but the center of the cytoplasm contains a clear area quite free from granules. In another place it will be shown that this type of abnormality is common in the human brain after fatal injuries with electricity.

Another stage in the recovery of the cell is shown in Figure 6. This rat survived the electric contact for 24 hours. The nucleus occupies a normal position and contains a swollen nucleolus. Granules are found around the nucleus, but one edge of the cytoplasm is quite free from granules and has a foamy, vacuolated appearance. The granules are not as large or well defined as in the normal cell.

Figure 7 shows a recovering cell with the nucleus in the normal position and with a swollen nucleolus. Many granules are present in the cytoplasm, although large, vacuolated areas are quite free from them.

A cell similar to that in Figure 6 is seen in Figure 8. The outer portion of the cytoplasm is relatively free from granules, whereas many are gathered around the nucleus.

The opposite arrangement of granules occurs in Figure 9. The

nucleus and nucleolus of the cell are normal. Nissl substance is appearing in the cytoplasm at the edges of the cytoplasm, but the central area around the nucleus has a vacuolated appearance.

Phagocytosis of injured and dead nerve cells is illustrated in the remaining three photomicrographs. The cell in Figure 10 has a swollen nucleolus but otherwise appears normal in structure. A phagocytic cell has, however, eaten deeply into the cytoplasm. Figure 11 shows a cell with a normal nucleus, but with a vacuolated cytoplasm containing a few dark-staining clusters of granules. The cytoplasm is being attacked by phagocytic cells. The nerve cell in Figure 12 is greatly shrunken; it stains a dark color and nucleus and cytoplasm can no longer be distinguished. It is surrounded by phagocytic cells.

SUMMARY

The nerve cell injuries that are discussed here involve both the nucleus and cytoplasm. The nucleolus is considered to be very resistant, but a marked swelling of this structure may be seen in the cells.

When death occurs immediately from electrical injuries many of the cells have nuclei that are shrunken and stain a uniform deep color so that nucleolus and chromatin strands may no longer be distinguished. The nucleus is often displaced to one side of the cytoplasm and is surrounded by a pale area indicating its former size. The suggestion is made that cells with deep-staining shrunken nuclei have no longer the power of recovery.

Abnormalities following less severe nerve damage are illustrated. The cytoplasm of the injured cells is shrunken and the perivascular space is large. Immediately following the trauma, there is a considerable decrease in Nissl substance and that which remains has lost its flaky appearance and looks coarsely granular. Often the edges of the cytoplasm appear to have no continuity, as if the cell had ruptured into the perivascular space. Swelling of the nucleolus occurs. A few hours after the electric shock the whole cytoplasm stains a uniform, deep color and no granules may be found. The Nissl substance is gradually reformed over a period of days, sometimes appearing first in the periphery of the cell and sometimes in the center around the nucleus. Restitution of the nucleus takes a longer time.

Cells that are injured beyond possibility of recovery become greatly

shrunken and cytoplasm and nucleus stain a uniform black color. Such cells are removed by phagocytosis.

The electrical current has a selective effect upon the nerve cells. Some anterior horn cells are greatly injured while others are fairly normal.

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OBSERVATIONS ON THE MENOPAUSE

III. Sensitiveness of Women at the Menopause to Epinephrine[1]

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With the Technical Assistance of Edith O'Donovan

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We have undertaken a study of 24 patients, chosen at random from women in or about the menopause in the out-patient department of Johns Hopkins Hospital, to determine their sensitivity to epinephrine, in conjunction with a study of the menopause syndrome.

In a study of the "Irritable Heart" in soldiers, Wearn and Sturgis (9) found evidence that the symptoms and signs in 60 per cent of their series of 73 patients were due to an irritable sympathetic nervous system. Following the intramuscular injection of 0.5 cc. of a 1 to 1000 solution of epinephrine hydrochloride, 43 of these 73 patients gave a reaction determined by definite standards as positive. Three of the remaining subjects gave a doubtful reaction.

The syndrome recognized as appearing at the climacteric in women, of which Culbertson (1) gave a very careful account, is certainly suggestive of a similar disorder of the autonomic nervous system. The flushings, cold hands and feet, erythema, excessive sweating, palpitation and dyspnea so frequently noted during the "change of life" bear witness to an instability of the controlling factors of the organism. The term "functional" is often applied to these symptoms. The hypertension of the menopause, so-called, which has been observed frequently to be a temporary phenomenon, has likewise been ascribed to the temporary functional disturbance in the organism's economy.

Hannan (4), using 10 minims of a 1 to 1000 solution of epinephrine hydrochloride intravenously, was able to produce in women complaining of flushes at the menopause an "attack of flushing which was, in all respects, identical with those attacks which occurred spontaneously." In three women at the menopause who were not complain-

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ing of flushings an identical injection of epinephrine produced a reaction similar to that in those complaining of flushings. As a control on these observations, Hannan injected into the same women "pituitrin" and normal saline, respectively, in place of epinephrine: in no instance were flushings reproduced by these injections.

In a series of patients, ten of whom were women at the menopause complaining of flushings and ten of whom were women at the menopause not complaining of flushings, 0.5 cc. of a 1 to 1000 solution of epinephrine was injected subcutaneously. The first group, *i.e.*, those who were complaining of flushings, showed a rise in systolic blood pressure of 12 to 25 mm. Hg. and an increase of pulse rate of from 7 to 10 beats per minute. Subjective symptoms were complained of by six of the ten women. The second group, consisting of women at the menopause who were not disturbed by flushings, showed no significant increase in systolic blood pressure, *i.e.*, above 5 mm. Hg., and no increase in pulse rate over 7 beats per minute, and suffered from no other disturbances during the period of observation. Hannan felt justified in concluding that there is an increased tonicity of the sympathetic nervous system which may be held accountable for many of the symptoms so commonly noted in women at the menopause.

METHOD

An injection was made subcutaneously into the deltoid region of the arm of 10 min. of a 1 to 1000 solution of epinephrine hydrochloride. In order to insure so far as possible the potency of the preparation, a fresh solution was prepared for each test, one tablet of $\frac{1}{200}$ grain of adrenalin to 1 cc. of sterile water, making a 1 to 1000 solution.

Before making the injection, the patient had been at rest in the recumbent position for at least thirty minutes. The women were told of the slight discomfort of the "needle." In addition, readings of the blood pressure and pulse rates were made at five-minute intervals until it was evident that the blood pressure and pulse rate had become stabilized at a resting level, before it was thought advisable to proceed with the experiment.

Blood pressure and pulse rate readings were recorded two or three minutes after the injection and then repeated at five-minute intervals for five or six readings and then at longer intervals, never exceeding ten minutes, until about fifty minutes after the injection.

The patient was not forewarned of possible subjective phenomena that might appear; for such data, reliance was placed on such information as the patient might volunteer. This varied, naturally, depending on the alertness and, above all, on the excitability of the patient. In addition, any objective response such as tremor and flushing was recorded, together with the time of appearance of these phenomena.

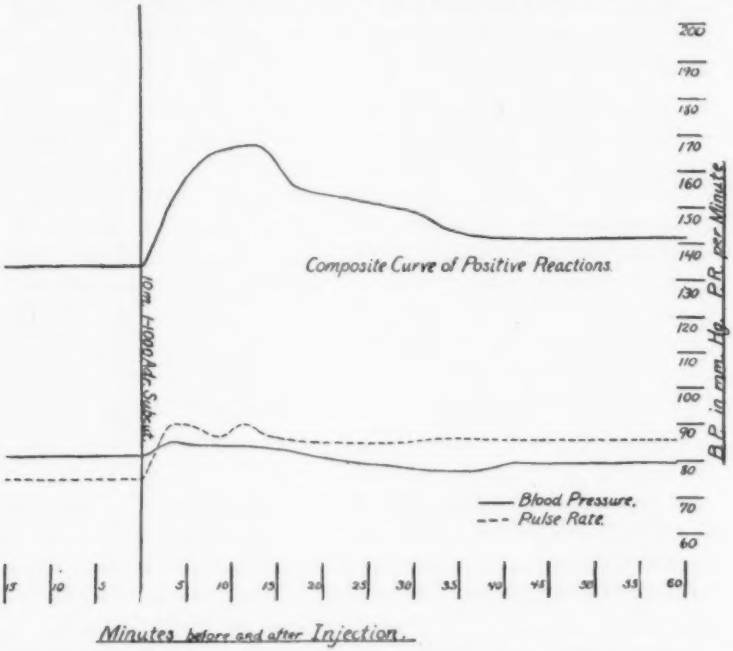
Composite Curve of Positive Reactions
10 m. 1:1000 Adr. Subcut.
Blood Pressure.
Pulse Rate.
B.P. in mm. Hg. P.R. per Minute
Minutes before and after Injection.

CHART 1. The composite curves of the responses of the twelve women who gave positive reactions. (Table 1.)

RESULTS

In reviewing the series of 24 cases, the reactions to adrenalin were found to be such that it did not seem necessary to lay down arbitrary standards as constituting a positive reaction. The cases seemed to fall conveniently into two groups, the characteristics of which were rather sharply defined.

Positive reactions. Of the 24 patients 12 gave a response such as we felt might be termed positive. In these positive reactions, there was an immediate rise in the systolic blood pressure reaching a maximum ranging from 25 to 70 mm. Hg. The maximal point was reached almost immediately in two cases; in five cases this high point was reached at the reading taken at the seven-minute period; in five cases the maximum was not attained until the twelve or thirteen-minute reading. The average rise in the systolic blood pressure was 38 mm. Hg., reached in an average of about eight minutes. From chart 1, which gives a composite curve of the twelve positive reactions, the mean rise is seen to be 33 mm. Hg. in twelve minutes.

The diastolic blood pressure curves show no constant immediate variation. In 5 cases, there was a rise of from 10 to 20 mm. Hg. within the first twenty minutes; in 4 cases there was a fall of from 10 to 15 mm. Hg. within a similar time and in 3 cases there was essentially no change in the diastolic level immediately after the injection. There seemed to be a tendency for the diastolic blood pressure to show a slight but almost invariable lowering later in the period of observation.

The pulse pressure, on the other hand, as would be expected from the marked rise in systolic pressure and the little change in the diastolic level, shows an average rise of 35 mm. Hg. reached in eight minutes, and a mean rise of 31 mm. Hg. reached in twelve minutes. The actual maximum change in the pulse pressure varied between 20 and 75 mm. Hg.

The pulse rate showed an average maximal rise of twenty-four beats per minute, reaching this maximum in an average of ten minutes. Two curves showed the maximal change in pulse rate to take place immediately after the injection. In 5 cases the high point was reached in seven to eight minutes and in 4 in twelve or thirteen minutes, while in one the peak was not attained until seventeen minutes after the injection. The increase in pulse rate varied between 9 and 36 beats per minute. The pulse-rate variation was usually transient, *i.e.*, the increase was rather sudden and the descent was equally as sharp: for this reason the broken line on chart 1 does not represent well what is obtained in the pulse-rate variations in individual cases. The mean variation shown on this chart is seen to be fourteen beats

per minute increase in twelve minutes. The tendency seemed to be for the pulse rate to stabilize itself at a level somewhat higher than the initial resting pulse rate as the period of observation was prolonged.

In one patient (No. 22: A. F.), there was a rise from an initial pulse rate of 78 to one of 96 almost immediately after the injection, with a

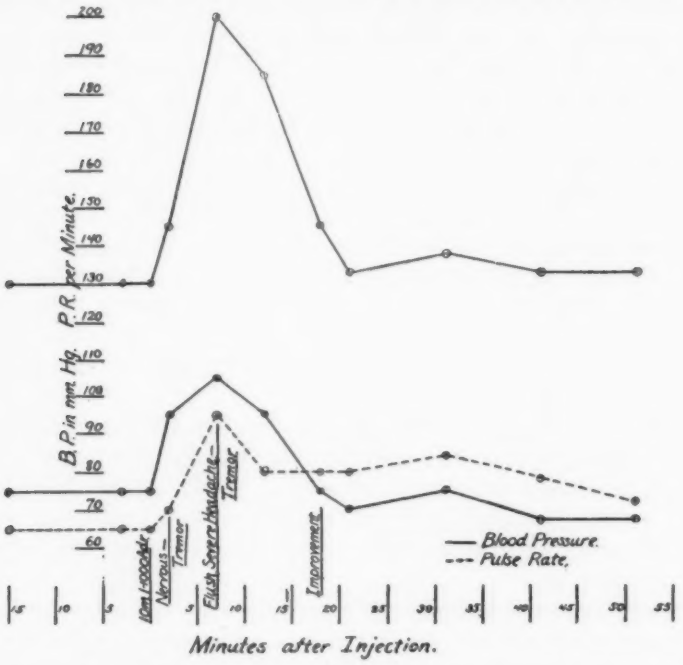

CHART 2. Patient No. 6. Active symptoms of the menopause have persisted for five years. There are two or three hot flushes daily at the present. A hot flush accompanied a violent reaction.

pulse that was irregular; the irregularity was the result of occasional "dropped beats." Regularity was established within a few minutes and the pulse rate reached 100 per minute.

In 11 of the 12 cases, definite, rather marked tremors were observed and invariably the patient complained of "trembling all over." In 7 cases, the patient remarked that she felt very nervous. Palpitation

was complained of in 6 cases. Two patients complained of weakness during the immediate reaction; following the period of observation, and, on arising, the patients complained of weakness almost invariably. Two women complained of a wave of chilliness over the whole body.

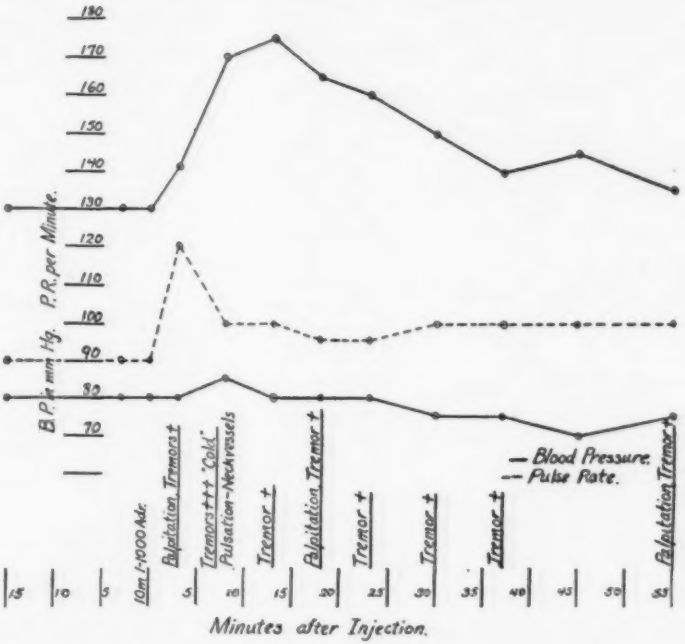

CHART 3. Patient No. 18. Symptoms of the menopause have been present for about one year. The patient reports six to eight hot flushes per day. The patient exhibited a definitely positive reaction.

One patient, who showed a rather marked reaction at the height of the attack, broke into a fit of crying without any obvious explanation.

In no case of the twelve was there a patient who did not complain of some of the above symptoms. In many of the cases the women volunteered the information that the injection reproduced the exact symptoms that had brought them to the dispensary.

Chart 2 shows the reaction of patient No. 6 (E. P.). At the peak of the rise in systolic blood pressure—a rise of 70 mm. Hg.—a flush was observed. The patient made the remark that this experience was identical with her frequent spontaneous flushes. Charts 3 and 4 reproduce the responses of patients No. 18 and 7, respectively.

Negative results. In 9 of the 24 cases, the reaction was definitely negative. The systolic blood pressure showed little or no change, as

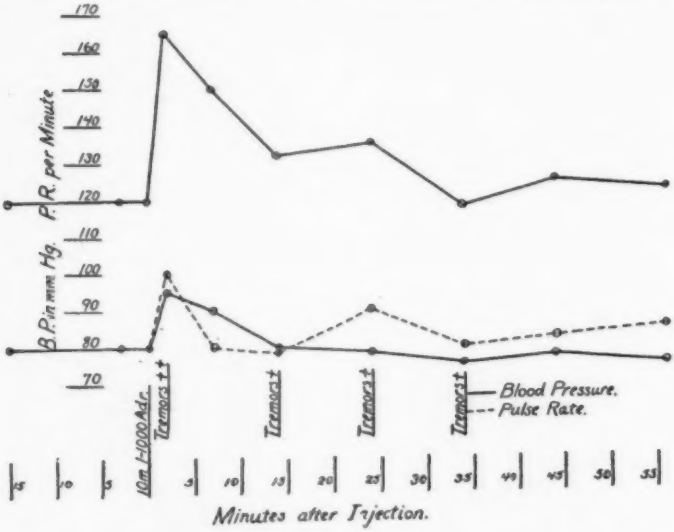

CHART 4. Patient No. 7. Symptoms of the menopause have continued for nine years following a bilateral oöphorectomy. The patient reports six to eight hot flushes per day. The response in this case was immediate.

is seen in the composite curve of these responses (chart 5). In but two cases was there noted a change of more than 10 mm. Hg. and in these there was a fall of 14 mm. in one and of 15 mm. in the other.

The diastolic level showed a more constant variation in that a fall of from 10 to 25 mm. Hg. was noted in 6 cases, with no essential change in the remaining 3 cases. The curve on chart 5 shows a gradual drop until about thirteen minutes following the injection, when the level reached was 12 mm. Hg. below the original reading. The diastolic

pressure seemed to stabilize itself then at this new lower level throughout the remainder of the period of observation.

The pulse pressure change was essentially equal to the change in the diastolic pressure in all 9 cases.

In 6 of the 9 cases the pulse rate was increased from 12 to 20 beats per minute; in 2 cases there was no essential change. The mean

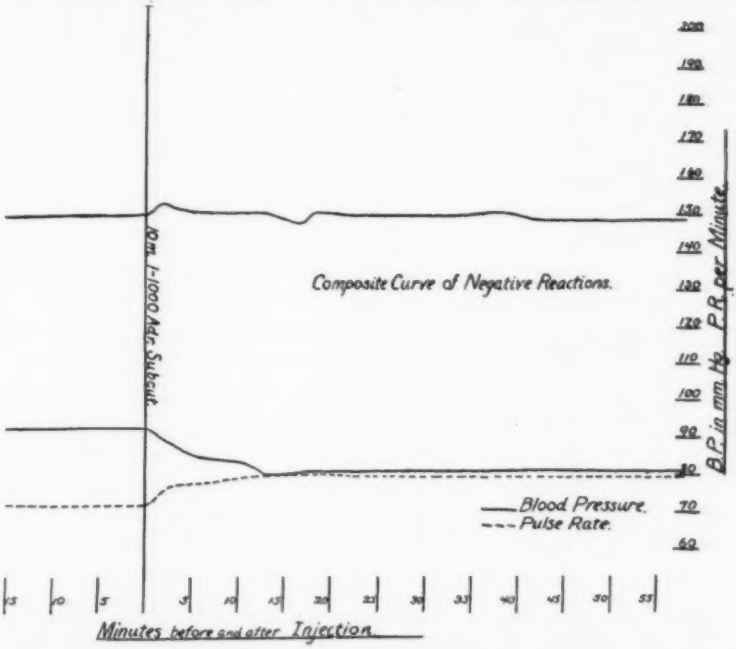
10 m. = 1000 Adv. Subcut.
Composite Curve of Negative Reactions.
B.P. in mm. Hg. P.R. per Minute.
Blood Pressure.
Pulse Rate.
Minutes before and after Injection.

CHART 5. The composite curve of nine women who gave entirely negative responses. (Table 2.)

increase in pulse rate was 15 beats per minute, an increase reached in nine minutes. Here again the pulse rate tended to find itself a new level as the period of observation was extended.

Two subjects experienced no subjective response to the injection. In 3 cases there was complaint of palpitation and nervousness. One woman complained of palpitation and showed some tremor, one patient

complained of palpitation, one of headache and one showed tremor. In none of these cases was the subjective response more than moderate.

Chart 6, which reproduces the response of patient No. 5, gives a fair example of what we have termed a negative response.

The remaining 3 patients of the series showed a systolic pressure which was increased 12, 14 and 11 mm. Hg., respectively, and a

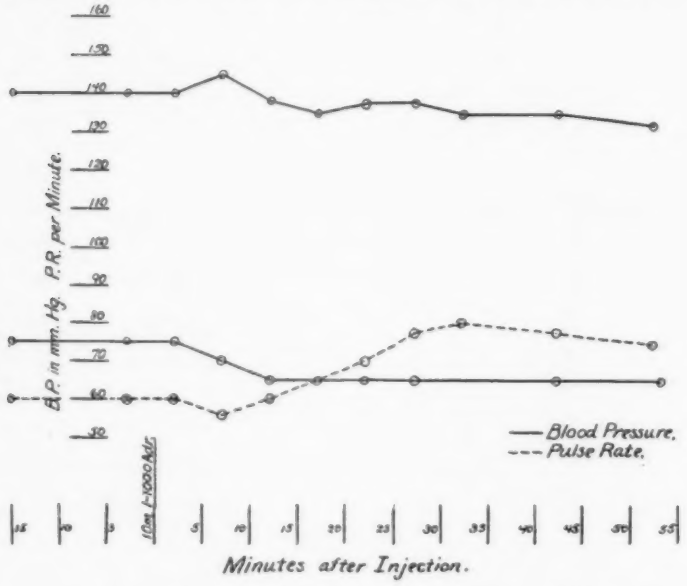

CHART 6. Patient No. 5. Symptoms of the menopause, which followed a bilateral oöphorectomy six years ago, have shown marked improvement. The response here was negative.

diastolic level which showed essentially no change in 2 cases and a fall of 10 mm. in 1 case. The pulse rate increased 22 beats per minute in 2 cases and fell 20 beats in 1 case. Two subjects complained of nervousness and showed tremors; the third had no abnormal symptoms nor signs.

Control observations. The response of the normal individual to epinephrine has been studied by numerous observers. Janeway (5)

demonstrated a pronounced rise in systolic blood pressure and in pulse rate following the intravenous injection of relatively large doses (m. xx of a 1 to 1000 solution) of epinephrine hydrochloride, with subsequent syncope requiring stimulants to restore the patient.

Petzetakis (8) made careful observations of the effect of intravenous injections of standardized solutions of epinephrine in a group of individuals between twenty and thirty-five years of age who showed normal cardiac rhythm and in whom no organic or vascular disease was demonstrable. Briefly, he found that doses of 1 cc. of solutions varying between 1 to 300,000 and 1 to 100,000 produced no objective disturbances. The use of 1 cc. of solutions of 1 to 60,000 to 1 to 20,000 usually resulted in immediate pallor and palpitations. Increasing the strength of the solution to 1 to 4000, he found that the subject invariably complained of dyspnea, palpitation and weakness; even syncope appeared imminent. With 1 cc. of a 1 to 1000 solution, syncope occurred so that cardiac stimulants were called upon!

Kylin (7), using 1 mg. of epinephrine subcutaneously, found a rise in blood pressure in normal individuals in one to two minutes, the maximum being 15 to 20 mm. Hg.! The maximal effect was observed in five to ten minutes. Vagotonic persons reacted with a preliminary depression of blood pressure and sympatheticotonic persons gave an exaggerated rise.

Injecting 0.5 cc. of a 1 to 1000 solution of epinephrine subcutaneously into women who reported normal menstrual cycles, Hannan (4) found no rise in systolic blood pressure over 8 mm. Hg. nor rise in pulse rate over five beats per minute. Likewise, subjective and objective phenomena were absent.

Using 10 m. of a 1 to 1000 solution of epinephrine subcutaneously, Goetsch (3) found that a slight reaction in apparently normal individuals was occasionally produced. With a larger dose (1 cc.), Clough (2) obtained moderate reactions in 50 per cent of normal individuals, marked reactions in 18 per cent, none in 32 per cent.

Following the same method as was employed with the women at the menopause, we determined the response to the subcutaneous injection of 10 min. of a 1 to 1000 solution of epinephrine in normal women. Ten, apparently healthy, white women between the ages of twenty and thirty volunteered for the test. Of these, four showed no

NUMBER	AGE	RACE	PRESENT WEIGHT	RECENT B.M.R.	RESTING B.P.	RESTING P.R.	OPERATIONS	MENSTRUAL	LAST MENSTRUAL PERIOD	EXCESS SWEATING
6	58	W.	156	−11	130/75	64	D & C, 1910 Mandible resection, 1916 Cholecystectomy 1922	Onset 17 Irregular Duration 3–6 Flow scanty	About 5 yrs.	0
7	32	W.	140	+1	122/80	80	T & A, 1916 App. 1918 Bilat. oöphor. and salp. 1919	Onset 16 Regular Duration 4 Flow average	9 yrs.	0
8	52	W.	145	−1	132/80	80	0	Onset 16 Regular Duration 8 Flow average	6 mos.	+
11	45	W.	114	±0	145/95	80	0	Onset 13 Regular Duration 3 Flow free	2 wks. No cessation	0
13	27	W.	154	−23	116/80	60	D & C, 1924	Onset 17 Regular Duration 3 Flow scanty	5 yrs.	0
14	52	W.	186	+6	150/85	70	0	Onset 11 Regular Duration 3–4 Flow average	1½ yrs. Irregular for?	+
16	47	W.	146	−10	120/80	78	D & C, 1905 R.R.V.O. 1912	Onset 13 Irreg. 5–6 wks. Duration 8 Flow profuse	18 mos. 2½ yrs. irregular Dec. flow and dur.	0
17	50	W.	138.6	−23	135/70	60	Amp. left leg, sarcoma (?) 1898	Onset 11 Irregular Duration 7 Flow profuse	8 yrs.	+

EXCESS SWEATING	VERTIGO	COLD HANDS AND FEET	HOT FLUSHES	DIZZINESS	ERYTHEMA	PALPITATIONS	DYSPNOEA	PRECORDIAL PAIN	APPROXIMATE DURATION OF SYMPTOMS	IMPROVEMENT IN SYMPTOMS	REMARKS
0	0	0	2–3 q.d.	+	0	+	0	+	5 yrs.	+	Mental irritability and depression. Obese.
0	+	+	6–8 q.d.	+	+	0	+	0	9 yrs.	0	Mental irritability and depression.
+	0	+	Occ.	+	0	+	+	0	6 mos.	0	Emotional instability.
0	0	0	0	0	0	0	0	0	5 mos.	0	Irregular menses three months. Irritability, depression.
0	0	+	q. month	+	0	+	+	0	5 yrs.	0	Obesity. Mild depression.
+	0	+	5 q.d.	0	0	+	+	0	3½ yrs.	+	Mental irritability.
0	+	+	1 q.d.	+		++	+	0	2½ yrs.	0	Obese.
+	0	+	4 q.d.	+		+	+	+	8 yrs.	+	Obese. Mild depression.

TABL

NUMBER	AGE	RACE	PRESENT WEIGHT	RECENT B.M.R.	RESTING B.P.	RESTING P.R.	OPERATIONS	MENSTRUAL	LAST MENSTRUAL PERIOD
18	50	W.	136	+12.5	130/80	90	0	Onset 15 Regular Duration 4–5 Flow average	3 mos.
19	46	W.	134	+3.5	140/95	75	App., Suspension of uterus, 1914	Onset 13 Regular Duration 3–4 Flow profuse	2 wks. P.M.P. 5½ mos.
22	45	W.	100	+10	155/80	78	T & A, 1917 Thyroid, 1922	Onset 13 Regular Duration 7 Flow average	Irregular for 2 yrs.
24	39	C.	186	±0	140/85	75	Hysterectomy Bilat. oöphor. and salp. 1928	Onset 14 Regular Duration 3 Flow scanty	1 yr.

change in systolic blood pressure; five gave an immediate rise of from 8 to 10 mm. Hg., and in one, the systolic blood pressure rose 15 mm. Hg. within eight minutes. In 4, the diastolic blood pressure fell 10 mm. Hg. within eight minutes; in 6 cases there was no essential immediate variation. The diastolic blood pressure in all these individuals showed a tendency toward a lower level during the period of observation. The pulse pressure varied accordingly, showing an average immediate increase of 10 mm. Hg. The average increase in pulse rate was 12 beats per minute. In 2 subjects, the pulse rate showed no essential change; in 3, the increase was between 10 and 12 beats per minute; in 3, the increase was between 16 and 18 beats per minute and in 2 individuals the pulse rate was increased 20 beats per minute immediately after the injection.

Palpitation was complained of by 8 of the 10 subjects. This was slight and of a transient nature in all cases. Three of the ten showed

TABL

ISTRUAL OD	VERTIGO	COLD HANDS AND FEET	HOT FLUSHES	DIZZINESS	ERYTHEMA	PALPITATIONS	DYSPNOEA	PRECORDIAL PAIN	APPROXIMATE DURATION OF SYMPTOMS	IMPROVEMENT IN SYMPTOMS	REMARKS
os.		+	6–8 q.d.	0		+	0	0	1 yr.	Slight	Diabetes. Slight depression.
ks. 5½	+	0	4–5 q.d. 1 year ago None now	+	0	+	+	0	2 yrs.	+	B.P. $\frac{210}{110}$ 8/27; gradual drop in 18 months.
r for 0	+	+	Occ.	0		++	+	+	2 yrs.	Slight	Irritability. Emotional instability.
r.	+	0	8 q.d.	+	0	0	+	0	1 yr.	0	Irritability. Emotional instability.

a slight tremor. In one individual, a temporary feeling of substernal pressure was noted. In one person, no objective nor subjective response was observed.

THE CLINICAL PICTURE

A clinical summary of the condition of the individuals on whom these observations were made has been prepared. An attempt has been made to give as clear a picture of the patient as possible when the observation of the reaction to epinephrine was made.

In table 1 are given the cases referred to as giving a positive response. Goetsch showed that in hyperthyroidism there is an increased sensitiveness of the sympathetic nervous system. In the twelve cases of our series in which positive reactions to epinephrine were obtained, only one showed a basal metabolic rate exceeding +10 and in this instance it was but +12.5.

NUMBER	AGE	RACE	PRESENT WEIGHT	RECENT B.M.R.	RESTING B.P.	RESTING P.R.	OPERATIONS	MENSTRUAL	LAST MENSTRUAL PERIOD	RECENT PREGNANCY
1	44	W.	110	+11	215/102	75	App. 1908 D & C, 1924	Onset 12 Regular Duration 4–5 Flow average	3½ yrs.	+
4	49	C.	185	−10	144/88	74	Hysterectomy Double S & O App. Apr. 1926	Onset 15 Regular Duration 3–4 Flow free	2½ yrs.	+
5	51	C.	122	+2	140/75	50	Hysterectomy Double S & O App. 1922	Onset 12 Regular Duration 3 Flow free	6 yrs.	+
10	54	W.	176	+3	155/100	65	0	Onset ? Regular Duration 3–4 Flow ?	3 yrs.	+
12	33	C.	208.5	−10	160/110	60	0	Onset 11 Regular Duration 3 Flow scanty	0	+
15	48	W.	167.5	−9	140/85	70	Bilateral oöphorectomy, 1924	Onset 16 Regular Duration 3 Flow average	4 yrs.	0
20	50	W.	101	+4.5	160/85	80	0	Onset 13 Regular Duration 4 Flow average	7 mos.	0
21	30	C.	216	−15	155/110	78	Hysterectomy Unilateral oöphorectomy, 1922	Onset 13 Regular Duration 2–3 Flow free	7 yrs.	+
23	54	W.	110	No recent B.M.R.	120/75	84	0	Onset 17 Regular Duration 4–5 Flow scanty	8½ yrs.	0

	EXCESS SWEATING	VERTIGO	COLD HANDS AND FEET	HOT FLUSHES	DIZZINESS	ERYTHEMA	PALPITATIONS	DYSPNOEA	PRECORDIAL PAIN	APPROXIMATE DURATION OF SYMPTOMS	IMPROVEMENT IN SYMPTOMS	REMARKS
yrs.	+	+		Rare	+		+	+	+	5 yrs.	+	Alcoholic. Mental irritability.
yrs.	+	0	+	5–6 q.d.	0	0	0	0	0	2½ yrs.	0	Menopause onset Dec. 1925. Opr. 1926.
rs.	+	0	0	0	0		0	0	Occ.	6 yrs.	+	
rs.	+	0		Rare	0	Occ.	0	Occ.		7 yrs.	+	
	+	0	0	0	0	0	0	Occ.		?		Obesity. B.M.R. −19, 7/24 to +4, 5/26.
rs.	0	0	+	Occ.	0	0	+	+	+	4 yrs.	+	Mental irritability. Some depression.
os.	0	0	+	Occ.	+		0	0	0	3–4 yrs.	+	Mild mental depression.
s.	+	0	+	None in past 2 yrs.	+	0	0	+	+	2 yrs.	+	Mental irritability.
rs.	0	0	0	0	0	0	0	0	0	9 yrs.	++	Mental irritability and depression.

TABL

NUMBER	AGE	RACE	PRESENT WEIGHT	RECENT B.M.R.	RESTING B.P.	RESTING P.R.	OPERATIONS	MENSTRUAL	LAST MENSTRUAL PERIOD	EXCESS SWEATING
2	47	W.	144	±0	122/82	70	0	Onset 14 Regular Duration 5 Flow average	No cessation	0
3	27	W.	201	+6	120/72	66	0	Onset 13 Irregular Duration 1–7 Flow irregular	2½ yrs.	0
9	51	W.	105	+7	158/90	64	App. 1915 Tonsil, 1917 Panhysterectomy, June 11, 1925	Onset 12 Regular Duration 3–4 Flow average	3 yrs.	0

In two of these women the menopause had been brought on artificially by operation. Both of these were relatively young at the time of the oöphorectomy and both of them had severe menopausal symptoms. In one of the two, the symptoms had continued in about the same degree of severity for nine years.

One patient (No. 22; A. F.) had undergone a thyroidectomy; it is of interest to note that this was the patient in whom the pulse irregularity was observed following adrenalin subcutaneously, as described above.

Of the whole series, four women thought there had been definite improvement in their symptoms prior to the test, while two others thought there had been some slight improvement.

One patient (No. 13; S.R.) came to us with a diagnosis of some "endocrine imbalance." She did not impress those who had seen her as myxedematous, in spite of her low basal metabolism. She had had an amenorrhea for five years following a five-year period of a relatively normal menstrual history. She presented definite complaints of hot flushes occurring at the time of the month when her menstruation was due.

EXCESS SWEATING	VERTIGO	COLD HANDS AND FEET	HOT FLUSHES	DEFINESS	ERYTHEMA	PALPITATIONS	DYSPNOEA	PRECORDIAL PAIN	APPROXIMATE DURATION OF SYMPTOMS	IMPROVEMENT IN SYMPTOMS	REMARKS
0	+	+	0	+		+	+	0	2½ yrs.	Slight	Emotional instability and irritability.
0	0	0	0	0	0	0	0	0			Mental irritability. Endocrine disorder.
0	0	+	1–2 q.d.	0	0	0	0	0	3 yrs.	+	Mild depression.

C. F. (No. 11) had as yet shown no cessation in her menses. She apparently was seen at the onset of the menopause. She had few symptoms; irregularity of menses had been noticed for three months. Yet her reaction was rather pronounced, with a systolic blood pressure rise of 70 mm. Hg., pulse pressure rise of 75 mm. Hg. and pulse rate increase of 36 beats per minute.

In table 2 are recorded 9 cases which gave a negative reaction. In these cases the basal metabolic rate seems of little importance. In three of these cases the menopause had been brought on artificially and in one other case bilateral oöphorectomy had been done four months after the onset of the symptoms suggesting a beginning menopause.

In all these cases except No. 4 (D. H.) there had been more or less marked decline in the menopausal phenomena. The one patient who was having more than an occasional flush showed a fall in systolic blood pressure of 8 mm. Hg., a fall in diastolic pressure of 20 mm. Hg., with no change in the pulse rate and no evidence, subjectively, of a reaction.

In the other three patients giving a negative response, one had been

submitted to artificial menopause. This patient alone of the three was having symptoms of the menopause.

Case No. 3 (T. N.) came to the menopause clinic diagnosed "Endocrine Disorder." She had practically no evidence of the menopause picture except an amenorrhea of two and a half years' standing.

Case No. 2 (E. G.) had had menopause symptoms for a period of two and a half years, although there had been no cessation of the menses.

DISCUSSION

No quantitive relationship between the reaction and the severity of the symptoms in the series of positive cases was obtained. However, this is as we should expect. The reaction is in a large part expressed in mm. Hg. change in blood pressure, whereas the measure of the severity of the symptoms depends upon what is told us by the patient. She may minimize or exaggerate her troubles, depending upon her general make-up. Whether her symptoms are increasing or decreasing in severity certainly influences the interpretation she puts upon the disturbances she experiences. The intelligence of the patient enters into the picture, inasmuch as it colors her description and observation of the character of such symptoms as the flushes. A patient may term six flushes a day as "three or four" or "every fifteen minutes." Since we can not observe the patient in a controlled environment such as we can supply during the course of the experiment, we are compelled to interpret the severity of the symptoms only in a general way.

We may visualize what occurs at the menopause as a period in which the glands of internal secretion are striving to rearrange their relative functional activity in the body's economy. With the onset of the menopause, the hitherto more or less balanced endocrine system is upset by the withdrawal of ovarian function either suddenly, as in the artificial menopause, or gradually, as in the natural onset of the menopause. With this loss, the other endocrine glands may be called upon to make certain alterations in their activity in relation to their former function.

The menopause varies in a number of ways, such as duration, severity and after-results, possibly depending upon pre-menopausal relationship of the glands of internal secretion. The part the ovary

plays in the balance before being removed may govern the nature of the compensation which will have to take place. The condition of the several glands may play some rôle in determining how much and how soon they will be able to assume the responsibility previously carried on by the functioning ovary.

Korenchevsky (6) found a lowered metabolism in fat dogs after castration, whereas in thin dogs such a procedure usually produced increased metabolism. He suggested that the varying degree of functional efficiency of the thyroid, hypophysis, adrenals and pancreas before castration played some rôle in determining the effect of castration.

It is relatively easy to understand how, during the endocrine upheaval, the response of so delicate a mechanism as the autonomic nervous system to stimuli might be disturbed. The sympathetic nervous system is more or less constantly presided over by certain members of the endocrine system. The absence of ovarian secretions in the body may cause a disorder of endocrine balance of a degree sufficient to upset the normal, smooth function of the sympathetic nervous system.

It seems safe to conclude that the symptoms in the menopause patient may be caused by hypersensitivity of the sympathetic nervous system, so that stimuli which, before the menopause, are insufficient to bring about any disturbance, may be followed during the menopause by very disagreeable sensations and phenomena.

In the group of soldiers with "irritable heart" studied by Wearn and Sturgis (9), the average maximal elevation of blood pressure occurred thirty-two minutes after the injection of epinephrine. As the maximal elevation in our series of positive cases was reached in an average time of about eight minutes after the injection, it seems very likely that the mechanisms underlying the reactions were different in the two groups.

Goetsch (3) has reported that the maximal reaction of hyperthyroid individuals who were sensitive to epinephrine occurs "early." This raises the interesting possibility that the positive reaction to epinephrine in hyperthyroid individuals and in women at the menopause, being in both instances presumably of endocrine origin, may be of

similar nature, while the sensitiveness to epinephrine of men with "irritable heart" is probable essentially different.

There was no evidence of hyperthyroidism in any of the women in our series who reacted positively to epinephrine. In one case, a previous hyperthyroidism may have been a feature of some importance. Hannan reports that basal metabolic tests were not done upon the women in his series of observations, but states that they showed no clinical evidence of hyperthyroidism. However, it seemed wise to us to do such a test routinely in order to eliminate the possibility that a positive response to epinephrine might be due to a hyperthyroid state. The basal metabolic rate in all our cases was normal, the highest being + 12.5 per cent.

It must be remembered that a borderline reaction (elevation of B. P. of 15 mm. Hg.) was obtained in one of ten young women who volunteered to act as control cases. However, no sharp reaction was obtained and the results from the "control" group are strikingly unlike those obtained from the women with symptoms of the menopause. In carrying out tests to determine sensitiveness to epinephrine, it would seem desirable to administer this preparation in dosage proportional to the body-weight. We did not do so, as we wished to use subcutaneously the same amount that Hannan and others had injected intravenously.

CONCLUSIONS

1. The menopause brings about in certain women a disturbance which causes them to give a "positive" reaction to epinephrine: this suggests that a hypersensitivity of the sympathetic nervous system may exist in a considerable proportion of women who suffer from symptoms of the menopause.

2. The distressing symptoms of the menopause may be the consequence of an increased irritability of the sympathetic nervous system.

3. There is no evidence that the positive reaction to epinephrine at the menopause is due to hyperthyroidism; however, the type of response obtained in women at the menopause resembles more closely the reaction of hyperthyroid individuals than that of men with "irritable heart."

4. The result of our observations of the effect of epinephrine by

subcutaneous injection upon women at the menopause are similar to those reported by Hannan. In Hannan's series there was a sharp difference as regards sensitivity to adrenalin between women at the menopause who had flushes and those who had none. In our series there were a number of exceptions to this rule.

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DEDICATION OF THE WILMER INSTITUTE

PROGRAMME

Tuesday, October 15, 1929

10.00 A.M. Dedication by President Joseph S. Ames.
Addresses by Herbert L. Satterlee, President of the William Holland Wilmer Foundation, by Mrs. Henry Breckinridge, and by Dr. George E. Vincent, President of the Rockefeller Foundation. (Wilmer Institute.)

11.30 A.M. Official Inspection of the Institute.
Signing of the Visitors' Book.

4.30 P.M. Tea (on the lawn).

5.00 P.M. Lecture on "The Development of Ophthalmology in Europe," by Hofrath Ernst Fuchs, of the University of Vienna. (Auditorium of the School of Hygiene.)

Wednesday, October 16, 1929

10.30 A.M. Lecture on "Some Contributions and Phases of American Ophthalmology," by Dr. George E. de Schweinitz, of the University of Pennsylvania. (Auditorium of the School of Hygiene.)

11.30 A.M. Inspection of the Institute.

2.30 P.M. Inspection (continued).

4.30 P.M. Tea (on the lawn).

5.00 P.M. Lecture on "Color Vision and its Anomalies," by Sir John Herbert Parsons, of the University of London. (Auditorium of the School of Hygiene.)

In the autumn of 1925 the Wilmer Ophthalmological Institute began its work, in cramped quarters and borrowed space, deferring the public celebration of its advent until a suitable building should be provided and equipped, and its various departments established and in use. The first surgical operation was performed on October 27, 1925, and since that time the Institute has served uninterruptedly as the Eye Clinic of the Johns Hopkins Hospital and the Department of Ophthalmology of the Johns Hopkins University Medical School.

During the summers of 1924 and 1925 Dr. Wilmer made an intensive study of the outstanding hospitals of Europe, in order that the new

Institute should include all of those advantages which European opthalmological centers had evolved. Plans were prepared by the architect, Joseph Evans Sperry, and in July, 1927, the building contract was awarded to the Fuller Construction Company of New York. The new building was completed about a year later, and occupied at once. The wing of the Hospital which had housed the Institute since 1925 was then reduced to little more than walls, remodelled entirely, and consolidated with the new edifice.

With its physical plant thus completed, plans for a formal opening were immediately prepared, and the time of the celebration set for October 15 and 16, 1929. Three of the world's leading ophthalmologists were invited to attend and deliver addresses: Hofrath Ernst Fuchs of the University of Vienna, representing Continental Europe, Sir John Herbert Parsons of the University of London, representing Great Britain, and Dr. George E. de Schweinitz of the University of Pennsylvania, representing the United States of America. Cordial acceptances from these distinguished scientists determined at the outset the success of the celebration. Some eight thousand announcements, and twenty-five hundred invitations, were sent out to individuals and learned societies in this country and abroad. Medical journals and newspapers devoted considerable space in their columns to the Institute and its plans, so that well before the autumn the news of the opening was widely disseminated.

On the morning of October 15 a large group gathered on the lawn of the hospital, where a stand had been erected for the guests and speakers. Beside the Trustees of the University, the Hospital, and the Wilmer Foundation, there were present many individuals distinguished in professional and public life, and a large number of Dr. Wilmer's personal friends and admirers. Many who could not attend the celebration expressed their felicitations with flowers, and the rooms and corridors of the Institute were filled with their fragrance and color.

The exercises were opened by Dr. Joseph S. Ames, President of the Johns Hopkins University, in the following words:

We have met here this morning to dedicate this Institute to the service of humanity and to do honor to the great investigator and physician whose name it bears.

The William Holland Wilmer Ophthalmological Institute combines an institution where every opportunity will be offered for the scientific study of the human eye and all the troubles to which it is exposed, with all the facilities known to us for the treatment of such troubles. From the former point of view the Institute is an integral part of the Johns Hopkins University; from the latter, of the Johns Hopkins Hospital. Its successful operation rests, however, in the hands of the man at the head of the Institute, and so long as Dr. Wilmer remains in charge, we will have no uncertainty as to the scientific knowledge which will be obtained in the laboratory nor as to the skill shown in the operating rooms. It must never be forgotten that any branch of medicine or surgery is both a science and an art.

This Institute owes its origin to the sympathetic understanding and imagination of a woman; she interested a large group of friends in her plan, and the William Holland Wilmer Foundation was the result; the coöperation of the University was offered, and in a short time the plan was realized, mainly by the generous support of the General Education Board. The existence today of this Institute is a striking evidence of the fact that success is assured to any project which combines a great idea, a man who can carry it into action and a place where the idea will be cherished.

On this day which sees the fulfillment of the hopes and wishes of so many people, I must congratulate first Mrs. Breckinridge; then her associates of the Wilmer Foundation; the University and Hospital; the students, faculty and staff who will work here; the patients who will come for help and comfort; but above all, Dr. Wilmer himself, who sees his dreams realized.

If such words are necessary, I hereby declare the William Holland Wilmer Ophthalmological Institute open and dedicated to the service of man.

Then followed the address of Mr. Herbert L. Satterlee, President of the William Holland Wilmer Foundation:

Those of us who came down from New York to take part in these exercises would have realized this morning the futility of preparing an address in advance, if we should have done so. We had pictured to ourselves an Assembly room filled by the friends of Dr. Wilmer and

Johns Hopkins University with the sunshine streaming in the windows. We find ourselves out of doors, under dripping skies with a cold wind blowing. However, it is such a happy occasion and the warmth of your Baltimore welcome has been so cordial that we forget about the weather.

The Wilmer Institute was made possible by the coöperation of the William Holland Wilmer Foundation, The Rockefeller Foundation and Johns Hopkins University. It is because I was chosen to succeed the late Robert W. Kelley as President of the Foundation, that I have the privilege of taking part in the dedication of the Institute. Yet, my friends, although this is the dedication of the buildings and the wonderful plant that has been provided for Dr. Wilmer's work, the *real* dedication took place when he and Mrs. Wilmer began their married life. They together determined that he should practice his profession in his chosen specialty for the benefit of all those who were suffering, without regard to their wealth or social position or the compensation which he might receive. It was because Dr. Wilmer helped everyone who came to his door, or to the clinic where he operated, without any regard to the material reward, that he gained the position which his professional brethren have long since accorded him and has rendered the service for which we all love and admire him. Mrs. Wilmer shared in the sacrifices which his high interpretation of his professional duty entailed as well as in those involved in Dr. Wilmer's distinguished service in the World War, and is also the recipient of our congratulations today.

We are honoured by the presence here of those ophthalmologists of international fame who have come from abroad and Dr. Wilmer's colleagues from all parts of the United States to help make this day happy for him.

It is a remarkable combination that has brought about the Wilmer Institute as part of the Johns Hopkins Hospital and Medical School, one of the great adjuncts of that splendid University which also bears the founder's name. We are dedicating buildings which, together with the equipment and endowment represent gifts of over $3,700,000. And yet it all came about in the most natural and simple way.

Sometimes a spring overflows and a little stream trickles down and joins itself with other streams and together they make a river. One

day gratitude in the heart of a woman welled over and Aida Breckinridge sought others whose sight had been saved by Dr. Wilmer. Banded together in the Wilmer Foundation the volume of their grateful affection grew and took practical shape. Like the waters of a mighty river, it is now transformed into power—power for the good of countless unnamed sufferers in the years to come. It is expressed in these buildings, in the clinic, the operating rooms, the research laboratories, in all the fine equipment which has been put at Dr. Wilmer's service. The splendid corps of loyal assistants, technicians and nurses who have been gathered around him are also part of the result of the dynamic energy of Mrs. Breckinridge's gratitude. So also is the endowment, thanks to the assistance of Dr. Vincent and Dr. Abraham Flexner, and the incorporation in the great university which was promoted by Mr. Kelley and Colonel Henry Breckinridge. Many other people have helped to make this day possible and some of them we are very glad to have with us today. It is really like a great family party, all centered around our beloved Chief and his wife. We all know that he will use what has been put at his disposal and employ his extraordinary skill and great experience in the years to come, as he has in the years past, in the same tireless, unselfish, reverent way that he always has done, for the benefit of his fellow men and the Glory of God.

From the inception of the Institute, Dr. Wilmer has indicated the need of establishing Fellowships in Ophthalmology in the University, so that gifted young physicians of limited means might remain for a reasonably prolonged period and lay the foundations for a subsequent ophthalmological career. One such Fellowship had already been established by the generosity of Mr. Adolph Lewisohn, and it was with great satisfaction that Mr. Satterlee was able to announce, at the end of his address, the gift of four similar Fellowships, the donors being Mr. Edward S. Harkness, Mr. Ira C. Copley, Mr. Andrew W. Mellon and his brother, Mr. William B. Mellon, and Mrs. Virginia Fair Vanderbilt.

The Institute, as Dr. Ames pointed out, "owes its origin to the sympathetic understanding of a woman," Mrs. Henry Breckinridge, who charmed her hearers with the intimate story of the Foundation's beginning, growth, and achievement:

I was asked to speak here this morning and consented only because I realized that it was a good opportunity to place credit where credit belongs. I am going to say a few words but I do not consider it a speech because I do not make speeches. I should just like to give you a brief picture of how the Wilmer Institute was started.

In 1922 when I was lying in bed with my eyes bandaged in a Washington hospital awaiting the outcome of the operation Dr. Wilmer had performed on my eyes, I had nothing better to do than interest myself in the general gossip of the hospital. The various nurses and doctors who made informal visits to my room told of the great number of Dr. Wilmer's patients who were coming and going all the time and how deeply indebted they felt for all that Dr. Wilmer had done for them.

I realized fully the many handicaps under which Dr. Wilmer was working in that small hospital from lack of equipment. I had heard several stories about the patients who, to express their appreciation of what Dr. Wilmer had done for them, established an ophthalmological clinic or added a wing in their home town hospital. I realized then that they would be just as willing to do the same for Dr. Wilmer. So I sent for Dr. Wilmer one day and told him what I thought about this. Dr. Wilmer admitted that such an institute was very much needed but was horrified at the suggestion that the financial aid of his patients be requested. He not only refused to give out a list of his patients but said he would block every attempt to compile a list.

We finally got a list together which was obtained by various methods. I communicated with opticians throughout the country asking for the names of patients who had come from Dr. Wilmer. I then got in touch with these patients and they proved more than willing to participate in this plan.

One of my most faithful aids was William, an old colored servant who had been in the Wilmer family for two generations. Every time I went to Dr. Wilmer's office William would have a few more names for me. At last we had a list of seven hundred and, of this number, three hundred and thirty-eight are responsible for the Wilmer Institute.

No form letter was used, as the Institute was to be built on appreciation, gratitude, and friendship, and each former patient was

approached personally. Some of those whom I approached would say that Dr. Wilmer didn't seem so enthusiastic. Then I'd have to begin all over again. I sat down and wrote individual letters to his various patients and out of it raised a sum of two or three hundred thousand dollars, in sums ranging from twenty-five thousand dollars down to a few dollars.

One contributor who was not a former patient of Dr. Wilmer's was Father John O'Sullivan, a chaplain during the War, stationed for a time at the flying center where Dr. Wilmer saw service. When the soldiers were wounded and dying, Father O'Sullivan would request a last message for their families, and when he returned to America after the War was over, he looked up some of the aviators with whom he had seen service in France and asked their aid in flying around the country to deliver to their families the last messages of the dying soldiers. A magazine writer learned about this and asked Father O'Sullivan to tell him the story which he used in his magazine. Father O'Sullivan received twenty-five dollars for the part he had played in having the story published. When Father O'Sullivan heard about the Foundation, he sent this money to me as his contribution.

Mr. Robert Kelley was our first President. During the time that I was without my sight in Washington, he was brought in to see me and after hearing my story offered me ten thousand dollars. I told him I was sure that if he had the opportunity to meet Dr. Wilmer he would appreciate the importance of raising this fund to make Dr. Wilmer free. He then asked me for that opportunity and they met that evening. As Mr. Kelley was walking out of my room at the Hospital, he turned to me and said, "Mrs. Breckinridge, I will raise the ante and guarantee your first hundred thousand." This was after seeing Dr. Wilmer, which proves that it was his leadership that built the Wilmer Institute; and through this guarantee Mr. Robert Kelley was made President of the Wilmer Foundation. During his life he did many things to help us put our large sum over the top and we feel that we owe him a great debt.

I went to the Rockefeller Board and presented the situation to them. They thought it was a very valuable idea but as there was no hospital in Washington sufficiently equipped to handle this thing, they wanted to know if Dr. Wilmer would be willing to tie himself

up with some large institution. If so, they might consider it. Then Mr. Breckinridge approached the Johns Hopkins University, and Dr. Wilmer consented to go to Baltimore; and the Rockefellers agreed, in that case, that they would give one and one-half million dollars if an equal sum was raised within three months.

Dr. Welch was very enthusiastic about having the Institute attached to the Johns Hopkins University. He would go to see anyone with whom I had made an appointment for him, and bring back a larger donation than the sum which I had suggested he might obtain. On one visit to New York, Dr. Welch heard of a man in Chicago who might be interested, and he caught the next train leaving for Chicago and brought back seventy-five thousand dollars.

One day in Washington I telephoned to one of our country's representatives and told him I was calling in the interest of the Wilmer Institute but he was not interested and the conversation terminated abruptly. I went around to see him and found him in a little office with no outlet other than the door through which I had entered so he had to listen to my story. I told him I had just telephoned to him and could not understand why he was not interested in the Wilmer Institute and he said he thought I had been talking about the Women's Institute. He had had so many requests from this direction that he was tired of the whole thing. But when he heard the name Wilmer his interest was aroused and he wanted me to sit down and tell him the whole story. Needless to say a donation was the result of this visit.

Another time, in answer to a telephone call from me, a certain person asked me to come to his office, and when I reached it one of the secretaries at an outer desk had a check for me. I, without knowing the amount of the check, refused to accept it because I hadn't been given the opportunity to tell this man the story. Sometime later this man sent for me and said he was interested in knowing all the details of the work that had been done to found the Wilmer Institute. After that second visit I received a check for forty thousand dollars from him and also the original check which I had refused to accept from his secretary and which was for one thousand dollars.

One of the strongest supporters was the secretary of one of the donors. She presented the idea to him, and followed it up at various times, in such a manner that his interest was held until the completion

of the Institute. This incident shows that it was not only people that gave money who built the Institute.

The Institute was founded on Dr. Wilmer's service to humanity. Everyone was interested in giving instantly when they heard his name. I hope now that he will have the opportunity to guide other men in his footsteps and impart to others some knowledge of his understanding of humanity. The purpose of the Institute is to carry on the philosophy of Dr. Wilmer by treating human beings as human beings and regarding the eye as the window of the soul.

In view of the very significant and generous part played by the General Education Board in the establishment of the Wilmer Institute, it was altogether fitting that the Rockefeller philanthropic organizations be represented in these exercises. The last address of the morning was made by Dr. George E. Vincent, President of the Rockefeller Foundation, and friend of Wilmer Institute, who spoke on "The Perpetuation of Personality":

It is difficult to avoid the clichés suggested by an occasion like this. One is almost compelled to quote: "An institution is but the lengthening shadow of an individual man." Yet like so many phrases, worn smooth by reverent repetition, this too needs a measure of correction and interpretation.

The "lengthening shadow" tends to grow more and more misty and to lose its implications of personality. How many, for example remember that Harvard, Yale, Vassar, even Johns Hopkins were the names of men? Such a fate will sooner or later overtake the name of Wilmer which today we honor. In a distant future it will have changed from a proper noun to a descriptive adjective.

Yet in spite of this knowledge in the background of our minds, we take keen satisfaction in celebrating the formal opening of this institute in the presence of the man who is its true creator. Here his skill and human sympathy find fitting expression; here they will have richer opportunities.

For the deeper meaning of this event one must search beneath the surface of names and conventional memorials. The thing that counts is this: the Wilmer Institute is a university clinic, not an isolated and individual project. A university is in essence not a group of

buildings with an endowment. It is a society of scholars which lives on generation after generation.

Within this society of teachers and learners, of searchers after truth, is perpetuated an ever growing, constantly reinterpreted tradition of knowledge, skill, beauty and aspiration. Here is a pooling of personalities, a communism of character and culture. Within this stream of onflowing association leaders live, make their contributions, and attain an immortality which becomes either anonymous or carries, for all but the initiated few, hardly more than the shadow of a name.

What stirs imagination and feeling today is the realization that Dr. Wilmer is to be a vitalizing, inspiring influence in this University environment. He has surrounded himself with men and women, investigators, specialists, laboratory assistants, nurses. Day by day his special knowledge, his skill, his insight into human ills and needs, his singularly sympathetic power in dealing with patients will permeate the group. Little by little, through example rather than precept, Dr. Wilmer's personality and gifts will, in a sense, be incorporated in other lives and through them pass on into the future years.

So at this hour we celebrate the opening not of a conventional memorial, not even the fame of a fine spirit, but the perpetuation of a rich personality through a comradeship of science and of service to mankind. Could Dr. Wilmer's modest devotion find more appropriate expression than in this clinic which will carry on into the long future not only his name, but what counts vastly more to him and to society, something of his insight, skill and sympathy to inform and inspire successive generations of investigators and physicians who will protect or heal countless men, women, and children through the long vistas of the coming decades and centuries?

Telegrams of congratulation were received from friends and institutions in all parts of the world. Of particular interest among them were the message of felicitation of President Hoover, and a radiogram from Commander Byrd in the Antarctic. After the dedicatory exercises, the guests signed the Visitors' Book and made an inspection of the Institute. Although Dr. Wilmer took no active part in the program, he issued the following statement to the Press:

This is the first institute in America devoted solely to ophthalmology, the study of everything which pertains to the eye or to vision. Heretofore Europe has led in this field of medicine, and our students have gone for their special training to the great clinics of London, Paris, Munich, Zurich, and Vienna. The generous founders of this Institute, convinced that the progress of ophthalmology in this country would be furthered by the establishment of such a center, have here provided facilities for study and treatment which I believe are not surpassed in the world today.

The work of the Institute falls under four general headings: the treatment of defective vision, investigation of the causes of eye troubles and the elaboration of new methods of combating them, research into the nature of vision—how and why we see, and the training of physicians, specialists, and nurses in the care of eye patients. All these activities are directed toward the same end, namely, the conservation of eyesight.

During the past four years, in spite of the difficulties attendant upon almost continuous building and lack of sufficient space in which to work, there have been performed, in temporary quarters mostly, approximately 2,200 major operations. During that period 4,500 patients have remained in the Institute for a study of the causes of their maladies, and for treatment. During the same period 45,000 new patients have been examined and treated in the Outdoor Department. These patients have come from nearly every state in the Union, which would seem to indicate that the Institute fills a need, not only local, but national as well. Thirty-eight articles on original research have come from the Institute's laboratories and clinics; three papers were presented by members of the staff at the International Ophthalmological Congress in Amsterdam this summer; and three of its graduates have been called to positions of distinction.

This short experience of the Institute's first four years of existence lead me to believe that it will justify the faith of its founders, and prove a contribution of value to the progress of ophthalmology.

THE HYDROLYSIS OF SODIUM HIPPURATE BY VARIOUS BACTERIA[1]

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The use of sodium hippurate as a test substance in differentiating types of streptococci was first described by Ayers and Rupp (1). The test has proven a valuable aid in such work, being simple and giving fairly definite results. It does not appear to have been extended to the study of bacteria other than streptococci, although there seems no reason to suppose that the test would not give useful information when so applied. The present work was therefore undertaken with the object of ascertaining the effect of various types of organism upon sodium hippurate and discovering its further possibilities (if any) as a differentiating substance.

EXPERIMENTAL

The test consists in cultivating the desired organism in a suitable medium containing the hippurate and then testing chemically for the products of hydrolysis. In the present study three sorts of medium were used; extract bouillon containing 1 per cent peptone, 3 per cent meat extract and 5 per cent sodium chloride and adjusted to a reaction of about pH 7.6; pork infusion bouillon made in the usual manner and having a reaction of about pH 7.6, and cooked meat medium prepared as described by Holman (2). All of the media contained 1 per cent sodium hippurate. Inoculation was made with a loopful of a 24-hour-old broth culture of the desired organism. Incubation of 48 hours was found to give unreliable results especially with the staphylococci. All tests for hydrolysis were therefore made after incubation for five days at 37°C. As a control, each tube of hippurate medium was paired with a tube of the same sort of medium containing no hippurate. Both were inoculated, incubated and tested at the same time and in the same way. Only tubes showing luxuriant

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TABLE I

Hydrolysis of sodium hippurate by various bacteria

ORGANISM	INCUBATION	
	24 hours	5 days
B. coli communis	−	−
B. coli communior	−	−
B. lactis aerogenes	−	+
B. alkaligenes		
3 strains	−	−
1 strain	−	±
B. bronchisepticus		
9 strains	−	+
B. proteus vulgaris	−	−
B. proteus mirabilis	−	−
B. typhosus (Rawlings)	−	−
B. typhosus (Hopkins)	−	−
B. typhosus E.	−	−
B. paratyphosus A (E-2)	−	−
B. paratyphosus A (E-3)	−	−
B. paratyphosus B	−	−
B. enteriditis	−	−
B. dysenteriae (Flexner) (E-7)	−	−
B. dysenteriae (Flexner) (E-3)	−	−
B. dysenteriae (Shiga)	−	−
B. of Friedländer	−	−
B. suipestifer	−	−
B. sanguinarium	−	−
B. of Danysz	−	−
B. aertryche	−	−
B. pullorum	−	−
B. pyocyaneus	−	−
B. prodigiosus	−	−
Sp. melchnikovi	−	−
Sp. cholerae	−	−

TABLE I—*Concluded*

ORGANISM	INCUBATION	
	24 hours	5 days
Sp. of hog cholera	−	−
Sp. of Finkler-Prior	−	−
Controls (sterile media)	−	−
B. pseudotetani		−
B. terminalis		+
B. fusiformis		−
B. laterosporus		−
B. centerosporus		±
B. subtilis		−
B. megatherium		−
B. anthracoides		+
B. anthracis		−
B. mesentericus encapsulatus		+
Controls (sterile media)		−
Cl. (vibrion) septique		−
Cl. welchii		−
Cl. tetani		−
Cl. sporogenes		−
Cl. histolyticus		−
Cl. botulinus		−
Controls (sterile media)		−
Staphylococci *aureus* and *albus* 39 strains*	Variable	+
Acne staphylococci 10 strains	−	+
Controls (sterile media)	−	−

* The staphylococci were tested after 20 hours', 48 hours', and 5 days' incubation. The 39 aureus and albus strains were found to give variable results after 20 hours and 48 hours, but gave constant positive tests after 5 days. The acne strains were all negative after 20 to 48 hours, but were also positive after 5 days' incubation.

growth were titrated. Tubes of sterile hippurate-containing and of hippurate-free medium were incubated and tested likewise. All tests were repeated and only in the case of some of the staphylococci was there any disagreement. In such cases longer incubation was found necessary, after which repeated tests gave consistent results.

For the detection of hydrolysis two methods are available. The addition of an acidified solution of ferric chloride will, in the presence of benzoic acid (one of the products of hydrolysis), give a flocculent precipitate. This method is subject to considerable error if the concentration of hippurate has varied appreciably for any cause, for example, from evaporation of water from the broth. Differences in the other constituents of the medium also affect the precipitate. Formol titration of the glycocol formed by the hydrolysis is not subject to these errors, and although possibly a little more troublesome, is regarded by us as the more reliable test. It is also roughly quantitative. The formol titration method "B" of Brown (3) was therefore used in this study for the determination of hydrolysis.

In reading the results of the titrations, if the hippurate culture of any organism required not over 0.3 cc. of NaOH more than the hippurate-free inoculated control it was considered "negative" (−); if between 0.3 and 0.5 cc., it was considered "doubtful" (±); if more than 0.5 cc., it was considered "positive" (+). This is an arbitrary standard. It is based, however, upon experience with streptococci, upon hundreds of tests carefully checked by the ferric chloride method and upon the present study. As in most biological procedures, it is difficult to draw a fine line of distinction between "positive" and "negative" reactions. The standard in this case is regarded as conservative. The results are given in Table I.

DISCUSSION

It is seen in Table I that, with the exception of *B. aerogenes* and *B. bronchisepticus*, the Gram-negative, aërobic, non-spore-forming rods studied are generally without action upon sodium hippurate. It was thought that *B. aerogenes* deserved further study. In Table II are given the formol titration figures for a number of strains of *B. coli* and *B. aerogenes* with controls of *B. alkaligenes*, *B. bronchi-*

septicus, staphylococcus and sterile media. The possible value of the test to sanitation bacteriologists need hardly be pointed out.

Of the staphylococci it may be said that they generally possess the power of hydrolyzing sodium hippurate, although this power may

TABLE II

Hydrolysis of sodium hippurate by strains of B. coli and B. aerogenes

Results of formol titration after 10 days' incubation expressed in number of cubic centimeters of N/20 NaOH required for 1 cc. of culture.

CULTURE	HIPPURATE BROTH	PLAIN BROTH	HYDROLYSIS OF HIPPURATE
B. coli			
H-1	0.80	1.00	−
H-2	0.90	0.90	−
H-3	0.75	0.70	−
H-4	0.85	0.90	−
H-5	0.85	0.80	−
H-6	0.75	0.85	−
B. lactis aerogenes			
H-7	1.95	0.90	+
H-8	2.00	0.90	+
H-9	2.25	0.85	+
H-10	1.65	0.80	+
H-11	1.00	0.55	+
H-12	1.25	0.65	+
H-13	1.45	0.70	+
H-14	1.35	0.70	+
H-15	3.30	0.70	+
Controls			
B. alkaligenes	0.75	0.75	−
B. bronchisepticus	1.20	0.75	+
Staphylococcus	2.70	1.00	+
Sterile media	0.75	0.85	−

vary considerably in different strains. Those obtained from acne lesions were found to be markedly slower in their action than any of the other strains. There seems to be no relation between pigment production and action upon sodium hippurate.

As regards the spore-formers, it is seen that a few members of the

aerobic group studied had some effect upon the test material. Of the anaerobes, all gave negative results. Inasmuch as only one strain, and that an old laboratory strain, of each organism was studied, no final conclusions regarding these organisms are justifiable at present.

It is hoped that the tabulated results may be useful to workers in various fields of bacteriology.

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(1) AYERS AND RUPP: *Jour. Infect. Diseases*, 1922, xxx, 318.
(2) BROWN, J. H.: *Jour. of Bacteriology*, 1923, viii, 245.
(3) HOLMAN, W. L.: *Ibid.*, 1919, iv, 149.

THE EDITORIAL POLICY OF THE JOHNS HOPKINS HOSPITAL BULLETIN

According to the Catalogue of the School of Medicine for 1930 the BULLETIN OF THE JOHNS HOPKINS HOSPITAL, issued monthly, contains articles by those connected with the School of Medicine and Hospital and the proceedings of the Medical Society. The original authorization in 1889 by the Trustees read: "The BULLETIN will contain announcements of courses of lectures, programmes of clinical and pathological study, details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures and all other matters of interest in connection with the work of the Hospital."

In accordance with these instructions we find in the first volumes of the Bulletin such subject matter as: A Brief Account of the Johns Hopkins Hospital; Officers of the Johns Hopkins Hospital; Training School for Nurses; Terms of Admission; Times of Meeting of Societies; Schedule of Lectures at the Training School for Nurses; Courses of Instruction for Graduates in Medicine; Schedule of Hours of Medical Instruction; List of Students in the Hospital; Report of the Superintendent of the Hospital, etc.

As one passes through each succeeding volume, it is apparent that "the other matters of interest in connection with the work of the Hospital" must have grown apace, for by the middle of the nineties, the BULLETIN is devoted almost exclusively to the publication of original investigations, excepting the continuance of the Proceedings of the Johns Hopkins Hospital Medical Society and Notes on New Books. Moreover, unlike most other journals, the BULLETIN published articles from all of the fields of medical science, clinical as well as preclinical. Many of the outstanding contributions in anatomy from the laboratory of Mall, for example, found their way into the BULLETIN. Besides these, the BULLETIN accepted papers from the cognate fields of public health and hygiene, as well as outstanding contributions to the history of medicine. With the establishment of the De Lamar and Herter lectures at the Johns Hopkins Medical School, the material of these was printed in the BULLETIN.

Thus the policy shaped itself of publishing the best investigations from all of the Departments of the Hospital and Medical School. It has been the aim of those conducting the BULLETIN to maintain this tradition.

It is of value, nevertheless, to pause to consider whether the BULLETIN is still adequately carrying out this policy. In all branches of medical science the investigations are tending to become more specialized, more technical. This is inherent in progress. This factor, although detracting from the general readability of the investigations, does not necessarily make them less valuable. This tendency in modern medicine has become reflected more and more in the pages of the BULLETIN—in the clinical perhaps even more than in the preclinical contributions. It is felt that this change is inevitable.

The BULLETIN is attempting to publish, and shall continue to do so, a certain number of articles of a more general nature and interest. Within this scope fall the Herter and De Lamar lectures, the addresses recently delivered by Dr. Cushing and Professor Sudhoff at the opening of the Welch Library, and the investigations which may be confidently expected from the newly established Department of the History of Medicine. An account of the origin and development of the William H. Welch Medical Library together with a description of the building and an account of the exercises held on the occasion of the dedication of the library and the inauguration of the chair of the History of Medicine appeared recently in the form of a special number of the BULLETIN inscribed to Dr. Welch. Records of such important medical events should become eventually of considerable historical interest. Similarly, contributions pertaining to the questions of medical education should properly find a place in the BULLETIN.

But mainly, by publishing the papers of not too great length from the laboratories and clinics of the Hospital and Medical School, the BULLETIN should continue to present the phases of scientific medicine which are engaging the attention of no small number of the present day investigators. Should the interests of to-morrow change, such an evolution would undoubtedly express itself in the pages of the BULLETIN. Its policy should be to reflect the best work of the time and in doing so to be guided by the prevailing interests rather than by too conscious an attempt to define what these interests should be.